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ORIGINAL ARTICLES

THE PREVALENCE OF PNEUMOCOCCAL TYPES AND THE CONTINUING IMPORTANCE OF PNEUMOCOCCAL INFECTION

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Concomitant with the improvement of therapy for pneumococcal disease, techniques for the efficient isolation and accurate identification of pneumococcus have been abandoned by most clinical laboratories. Serums for the determination of pneumococcal capsular types have become increasingly difficult to obtain and within the past year, the last source of these materials has ceased to make them available commercially. As a result of these events, knowledge concerning the incidence and nature of pneumococcal disease is waning, and one hears frequently in the United States, Great Britain and continental Europe statements to the effect that pneumococcal disease is no longer as prevalent as it was prior to the advent of antibiotics. A similar point of view was held widely in the area in which this study was conducted until pneumococcal typing was reintroduced as a routine laboratory procedure in 1952. The data accumulated since that time form the basis of the present report and indicate that pneumococcus continues to be an important cause of disease in man.

Materials and Methods. The patients studied were those admitted to the 225 beds of Division II Medical Service (State University Division) of Kings County Hospital, Brooklyn, New York, with acute disease of the respiratory tract or with fever of unknown origin. Approximately two-thirds of these individuals had pneumonia.

At the time of admission, sputum was collected in a sterile glass jar with a screw cap. When sputum was unobtainable, cultures of the nasopharynx and oropharynx were taken with swabs moistened with sterile broth. Blood for culture was obtained usually from an antecubital vein and inoculated into trypticase soy broth and Brewer's thioglycollate medium at the bedside.

Sputum was handled in the following manner upon receipt in the laboratory: A smear was made and examined microscopically after staining by the Gram technique. A loopful was then streaked upon the surface of a nutrient agar plate containing 10% equine or human blood. The sputum was then emulsified by refluxing in a sterile 2 ml. syringe with or without the addition of a small amount of sterile broth and 1 ml. of the emulsion was injected into the peritoneal cavity of a mouse. All mice surviving were sacrificed at the end of 4 days after inoculation in accordance with the observations of Mørch[9], who was able to recover pneumococci from 5% of animals surviving infection this period of time. Upon death of the animal, a necropsy was performed with sterile technique and

cultures were made of cardiac blood and of peritoneal washings obtained with sterile normal solutions of sodium chloride. In addition, peritoneal washings were used to provide material for typing.

Swabs of the naso- and oropharynx were incubated for several hours in 5 ml. of neopeptone broth containing 0.1 ml. of defibrinated rabbit's blood. After incubation, 1 ml. of the culture was inoculated intraperitoneally into a mouse and a loopful of culture was streaked on the surface of a blood agar plate.

Blood cultures were incubated at 37° C. and examined daily for evidence of bacterial growth. Smears and subcultures were made when indicated.

Cultures on blood agar plates were examined under a modified dissecting microscope at a magnification of 45× and cells from colonies resembling those of pneumococci were isolated with a sterile needle or loop. These cells were inoculated into neopeptone-rabbit's blood broth or onto other blood agar plates to provide bacteria for further study.

Typing of pneumococci was carried out with the Neufeld technique.* The details of the procedure for the quellung reaction are set forth elsewhere (Austrian and Austrian[1]).

Classification of organisms failing to give a quellung reaction as untypable pneumococci was based upon their morphologic and cultural characteristics, their lysis in 1% sodium deoxycholate and their virulence for mice.

Results. In Table 1 are shown the number and types of pneumococci isolated from adult patients in the 5-year period from October 1, 1952, to September 30, 1957. In all, 1354 strains of pneumococci were recovered from 1322 patients. The somewhat smaller number of recoveries in the first year of the study may reflect the position of the laboratory, which was located then in a building remote from the wards, rather than a true lower incidence of pneumococcus in that period. The distribution of types in order of frequency is shown in Table 2.

Table 3 records the incidence of bacteremia caused by the several types of pneumococci during the same period. With the exception of the first year of the study, pneumococcal bacteremia was found to be present, on the average, in about 45 patients a year.

Several facts of interest emerge from the data. Of the 1354 strains of pneumococcus isolated, 48.8% comprise organisms of types I to VIII inclusive. Of the pneumococcal bacteremias, 66.7% were caused by organisms of these same capsular types. It would appear, therefore, that the preponderance of serious pneumococcal infections in the period designated were caused, with the exceptions to be noted, by organisms responsible for the majority of infections in man in the era before antibiotics became available.

The high incidence of strains of pneumococcus type III results probably from several factors: the ease with which this organism may be recognized on the surface of blood agar plates, its high virulence for white mice and its not infrequent presence in the upper respiratory tract of carriers. The large number of strains of type VII is of interest, the emergence of this type as an important cause of pneumonia having been noted over a decade ago by Thompson *et al.*[11]. The rarity of pneumococcus type II is striking, for it is the twenty-ninth in frequency among the first thirty-three pneumococcal types. Its invasive properties, however, are manifested in the infections caused by it. Of 7 cases of type II pneumococcal lobar pneumonia, 5 were accompanied by bacteremia. Another highly invasive pneumococcal type was type XII. The pathogenicity of this type for man has been pointed out by Hodges and MacLeod[7].

Bacteremia was present in 14.8% of the patients from whom pneumococci were isolated. Approximately two-

*Capsular typing serum was made available through the courtesy of Dr. H. D. Piersma, Lederle Laboratories Division, American Cyanamid Company, of Dr. E. F. Roberts, Wyeth Laboratories, American Home Products Corporation, and of Dr. Erna Lund, Statens Serum-institut, Copenhagen.

TABLE 1.—PNEUMOCOCCAL ISOLATIONS FROM OCTOBER 1, 1952, TO SEPTEMBER 30, 1957

	Number of Strains Isolated					
Type	*1952–53*	*1953–54*	*1954–55*	*1955–56*	*1956–57*	*Total*
1	15	35	22	24	4	110
2	2	0	3	1	1	7
3	24	37	26	23	58	168
4	11	20	12	19	18	80
5	2	12	4	4	6	28
6	4	16	13	7	24	64
7	10	39	23	24	23	119
8	8	15	16	16	30	85
9	3	5	4	9	20	41
10	3	3	3	0	5	14
11	3	17	2	6	6	34
12	8	15	7	6	9	45
13	2	9	4	5	8	28
14	6	5	6	10	8	35
15	2	4	1	1	5	13
16	4	6	1	3	5	19
17	3	11	8	10	12	44
18	3	13	15	4	9	44
19	2	13	14	6	18	53
20	4	13	5	8	4	34
21	1	2	5	1	6	15
22	2	6	5	8	16	37
23	3	5	5	5	10	28
24	0	3	4	0	5	12
25	1	3	1	0	3	8
27	2	0	0	1	0	3
28	1	5	4	2	4	16
29	6	6	3	4	2	21
31	4	3	4	1	1	13
32	0	1	0	2	1	4
33	6	8	1	4	6	25
Untypable	10	29	13	27	28	107
Total	155	359	234	241	365	1354

TABLE 2.—DISTRIBUTION OF PNEUMOCOCCAL TYPES 1952–57

Type	*Number*	*Type*	*Number*	*Type*	*Number*
3	168	22	37	21	15
7	119	14	35	10	14
1	110	11	34	15	13
8	85	20	34	31	13
4	80	5	28	24	12
6	64	13	28	25	8
19	53	23	28	2	7
12	45	33	25	32	4
17	44	29	21	27	3
18	44	16	19	Untypable	107
9	41	28	16		

thirds of these individuals had pneumonia. If the rate of bacteremia be adjusted to this latter observation, it becomes 23%, a figure in keeping with those reported previously (Austrian and Rosenblum[2], Austrian and Winston[3]). The occurrence of approximately 180 cases of pneumococcal pneumonia in a year on a medical service of 225 beds is indicative of the continuing importance of pneumococcal infection.

In 1957, serums for the identification of certain of the higher pneumococcal types became available. To designate them, the nomenclature of Eddy will be employed[4]. Because monovalent serums for some types were lacking, these types are grouped with others from which they could not be distinguished with the reagents available. Figures for the incidence of isolations for all types for the calendar years 1957 and 1958 are shown in Table 4 and those for pneumococcal bacteremia for the same periods are listed in Table 5. The relative lack of invasiveness of the higher types is evident from the rarity of bacteremia caused by these organisms. In a period of 6 years, pneumococci of types other than the first thirty-three have been recovered from the blood of patients in only 10 instances. Of the higher pneumococcal types isolated from the respiratory tract, type XLI has been the most common. The availability of the additional serums has reduced the percentage of untypable strains from 8 to 2.7.

The relation of pneumococcal bacteremia to the outbreak of influenza in 1957 (Widelock *et al.*[12]) is of some interest. There were 12 cases of pneumococcal bacteremia in the month of October, 1957, in contrast to a usual incidence of 4 or 5 cases in that month. In the same period, pneumococci were isolated from 63 patients.

Extrapulmonary infection with pneumococcus was relatively infrequent in the initial 5-year period of the study. There were 26 cases of meningitis, 10 cases with pleural empyema and 6 with proved or suspected endocarditis. Only 2 cases of pneumococcal arthritis were observed in the same interval.

TABLE 3.—PNEUMOCOCCAL BACTEREMIA 1952–57

Type	*Number*	*Type*	*Number*	*Type*	*Number*
1	40	17	6	10	2
7	31	19	6	16	2
3	19	2	5	21	1
8	19	6	5	22	1
12	18	5	4	25	1
4	17	20	3	33	1
14	9	23	3	Untypable	7
18	7	9	2	Total	209

Discussion. The data presented provide evidence of the continuing importance of pneumococcus in disease of the human respiratory tract and of the fact that there has been relatively little change in the distribution of pneumococcal types responsible for the majority of infections in man. The most notable exception to the latter statement is the rarity, in the 6 years for which figures are available, of infection caused by pneumococcus type II. Variations in the incidence of infection caused by this organism have been recognized in the past (Griffith[5]).

There are only three ways in which isolation of pneumococcus from the upper respiratory tract can be associated with certainty with infection

in man. They are isolation of the same organism from the blood, recovery of the organism from an area of consolidation by puncture of the lung or demonstration of a rise in the titre of antibodies to organisms of the same capsular type. Of these, the most simple is the identification of bacteremia when present. In this study, pneumococcal bacteremia has been recognized, on the average, in 45 patients annually among those admitted to the medical service. Pneumococcus, therefore, remains among the most important causes of infection of the blood stream today. That the course of infection has been altered since antibiotics have been used in the treatment of it is obvious to all. Treated soon after onset, pneumococcal pneumonia may be limited to a single pulmonary segment rather than progressing to the involvement of an entire lobe or beyond it. In addition, the incidence of extrapulmonary complications has been reduced strikingly. According to Heffron[6], empyema was associated with type I pneumococcal pneumonia in 7.4% of those cases without bacteremia and in 18.8% of those cases with bacteremia before antibiotics were available. In the present series of 110 infections caused by pneumococcus type I, of which 40 were accompanied by bacteremia, there was not a single case of empyema. These facts notwithstanding, patients arriving

TABLE 4.—PNEUMOCOCCAL ISOLATIONS 1957–58

Type	*Number*	*Type*	*Number*	*Type*	*Number*
1	25	17	27	34	11
2	5	18	28	35,47,66	11
3	96	19	53	36	1
4	43	20	20	38.74	4
5	14	21	9	39,40,42,72	11
6	53	22	27	41	21
7	49	23	21	43,53	11
8	61	24	10	44,55,56	4
9	53	25	3	45	3
10	13	27	0	46.64	13
11	16	28	8	48,50,51	10
12	22	29	10	57.58,59	5
13	18	30,54	9	61	4
14	28	31	8	71	1
15	11	32	5	72	1
16	11	33	11	Untypable	25
		Total	903		

TABLE 5.—PNEUMOCOCCAL BACTEREMIA 1957–58

Type	*Number*	*Type*	*Number*	*Type*	*Number*
8	17	18	4	10	1
1	14	20	4	13	1
3	13	2	3	15	1
7	11	6	3	23	1
4	10	22	2	44,55,56	1
12	10	25	2	46,64	1
5	5	30,54	2	72	1
14	5	33	2		
19	5	9	1	Total	120

at the hospital in the advanced stages of pneumococcal infection continue to present many of the manifestations noted before effective antibacterial therapy became available and to succumb to the disease. In 1957, five patients with pneumonia and bacteremia and 3 with meningitis died.

It is an interesting paradox that, having obtained highly effective drugs with which to treat pneumococcal infection, the medical profession has abandoned largely the laboratory techniques necessary to establish an etiologic diagnosis. The reasons for this appear to be, in the main, ones of economy. The methods for the isolation and identification of pneumococcus are among the most precise and efficient ones developed by bacteriologists. If physicians are to have an accurate picture of the causes of respiratory disease, it will be necessary that satisfactory diagnostic methods be reintroduced (Hodges, MacLeod and Bernhard[8]). The most pressing need is for a source of pneumococcal typing serum. Under existing conditions, it would appear probable that these can be obtained only through the support and interest of some governmental agency. Until such serums do become available once more, it is probable that mistaken ideas about the etiology of pneumonia will persist and that misdiagnosed "virus" pneumonia will continue to respond to treatment with antibiotics.

As pointed out by Reimann[10] nearly a decade ago, the incidence of pneumococcal disease in American urban populations shows, in the absence of social upheavals, remarkable constancy. The material presented in this communication is entirely consistent with the view that pneumococcus continues to be an important cause of bacterial pneumonia in such an area today.

Summary. Data have been presented relating to the isolation of pneumococci from patients on a general medical ward service for the 5-year period from 1952 to 1957. In all, pneumococci were recovered from 1322 patients, of whom approximately two-thirds had pneumonia. Of the strains isolated, 48.8% were included in capsular types I to VIII inclusive and two-thirds of 209 pneumococcal bacteremias were caused by organisms of these same capsular types. The observations reflect the continuing importance of pneumococcus as a cause of disease in man. They point also to a need for the reintroduction of capsular typing serum and of satisfactory laboratory techniques for the isolation and identification of pneumococcus if an accurate understanding of the causes of pneumonia is to be realized.

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SUMMARIO IN INTERLINGUA

Le Prevalentia del Typos de Pneumococco e le Continue Importantia de Infectiones Pneumococcal

Es presentate datos relative al isolation de pneumococcos ab patientes de un servicio medical general, effectuate durante le quinquenne periodo ab 1952 a 1957. In summa, pneumococcos esseva obtenite ab 1322 patientes. Circa duo tertios de istes habeva pneumonia. Quanto al racias isolate, 48,8% del numero total esseva includite in le typos capsular I a VIII, e duo tertios de 209 casos de bacetremia pneumococcal esseva causate per organismos de iste mesme typos capsular. Iste observationes indica le continue importantia de pneumococcos como causa de morbos in humanos. Illos signala etiam le desirabilitate de re-introducer sero pro le typation capsular e satisfacente technicas laboratorial pro le isolation e identification de pneumococcos si un accurate comprension del causas de pneumonia es ancora recognoscite como un major objectivo del investigation medical.

SUMMARIO IN INTERLINGUA

(See page 146 for original article)

Le Uso de Assistentia Mechanic in le Tractamento de Morbos Cardiopulmonar

1. Le uso de un cinctura abdominal que es rhythmicamente inflationate e que functiona in alternation con un pression positive de inspiration applicate al bucca se ha provate efficace in le ventilation de patientes con sever emphysema pulmonar. Le methodo contribue al reduction del hyperdistension, illo reduce le tension alveolar de dioxydo de carbon, e in casos de instabilitate vasomotori illo mantene le tension del sanguine.

2. Un apparato que provide un rhythmo alternante de electrostimulation neuromuscular del diaphragma e del musculos infero-abdominal es similemente capace a effectuar un adequate ventilation de patientes emphysematose. Illo pare esser promittente como instrumento pro le initiation de exercitios de respiration diaphragmatic in patientes in qui un morbo ha vitiate le motion del diaphragma.

BONE MARROW NEEDLE BIOPSY

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In 1958 McFarland and Dameshek[5] described a simple, bedside technique for obtaining a bone marrow biopsy, using a Vim-Silverman needle[8]. During the past year a slight modification of this method has been used in this laboratory with excellent results, and it is felt that this type of needle biopsy should be considered the bone marrow biopsy method of primary choice. This procedure should eliminate almost completely the necessity for performing a surgical bone marrow trephine.

Materials and Methods. A. PATIENT GROUP. In the course of performing 100 bone marrow aspirations it was necessary to perform 20 marrow biopsies. These patients ranged in age from 26 months to 85 years. In the majority of the patients the biopsy was done after one or more attempts by needle aspiration were unsuccessful. Many of these patients were either so seriously ill or chronically debilitated that it would have been inadvisable to move them even for minor surgery.

B. BIOPSY INSTRUMENT. A 3½ inch, 16 gauge, Vim-Silverman needle with the cutting blade protruding ⅝ in. beyond the needle tip was used. An ordinary liver biopsy needle was cut to these specifications.*

C. TECHNIQUE. The posterior superior iliac spine was the site of biopsy in all instances. The method used for positioning the needle was that described by Bierman and Kelly[1] for marrow aspiration. The posterior superior iliac spine is located by inspection and palpation (Fig. 1). Not infrequently, simple inspection reveals its prominence, but usually it is necessary to follow the iliac crest to the point of its posterior termination. Intersecting thumbnail pressure marks on the skin over the proposed point of needle entry may be a helpful guide and are made before cleansing the skin with iodine and alcohol. Two to 4 ml. of 1% procaine are sufficient for adequate anesthetization of the soft tissues and periosteum. After the procaine is injected the biopsy needle, with obturator in place, is introduced into the posterior superior iliac spine, and with a gentle rotary motion is advanced into the bony cortex. As soon as the "give" signifying penetration of the bony cortex is felt, the obturator is removed and the cutting blade inserted. Occasionally some degree of force may be necessary to do this. The outer sheath then is advanced over the cutting blade as in the liver biopsy technique (Schiff[7]). Then, holding both the cutting blade and the sheath, the needle is given a rapid ½ turn in a clockwise direction and removed *in toto*. The forked cutting blades are carefully separated with a hypodermic needle and the tissue is removed.

D. HANDLING OF SPECIMEN. The tissue, while attached to the tip of the hypodermic needle, is touched at multiple sites to the surface of several clean #1 cover glasses, dropped into 10% formalin solution for 24 hours, and decalcified overnight in a nitric acid-formaldehyde solution.† The tissue then is stored in 70% alcohol until such time as it is embedded in paraffin, cut at from 3 to 5μ, and stained with either Giemsa or hematoxylin and eosin stains.

*This was done by Charles Archer, Shore Road, R.F.D. #1, Westerly, R.I.

†Nitric acid 100 ml.
Formaldehyde (40%) 100 ml.
Distilled water 900 ml.

Results. The results of this study are summarized in Table 1. Bone marrow needle biopsy was performed on 13 patients whose marrow aspirations resulted in "dry taps," Six of the patients had marrow infiltration with either lymphoma or leukemic cells, 3 showed hypoplasia of the bone marrow with fatty replacement, and 2 revealed myelofibrosis (Fig. 2). Of the 2 remaining cases one was a patient with thrombocytopenic purpura whose marrow aspiration had been unsuccessful. However, bone marrow biopsy indicated that the marrow was very cellular, with an increase in immature megakaryocytes. In this instance, therefore, the correct diagnosis of idiopathic thrombocytopenic purpura rather than that of a secondary or "toxic purpura" was established. The other patient had a bone marrow which revealed depression of the erythroid elements.

Bone marrow biopsy was performed on 4 patients with suspected granulomatous disease. No granulomas were found, but adequate tissue for their detection was obtained. In another instance metastatic carcinoma was suspected in a patient because of an osteoblastic area noted in the vertebral column by Roentgen ray. Neoplastic cells were demonstrated in this section (Fig. 3). One biopsy was performed on a patient who, by aspiration, was noted to have extensive eosinophilic, lymphocytic, and plasmocytic infiltration of the marrow. The biopsy showed this to be a diffuse and generalized process without neoplastic or granulomatous invasion. It also should be mentioned that the procedure was performed without difficulty on a 26-month-old child whose bone marrow was markedly hypoplastic.

Examination of the touch prepara-

TABLE 1.—RESULTS OF BONE MARROW NEEDLE BIOPSY

Reason for Biopsy	*Diagnosis*	*No. of Cases*
	Leukemic or lymphomatous infiltration	6
Dry tap	Myelofibrosis	2
	Hypoplastic marrow	3
Inadequate aspiration smear for diagnosis	Idiopathic thrombocytopenic purpura	1
	Normal bone marrow	1
	Normal marrow	4
Possible marrow infiltrate with tumor or granulomata	Metastatic carcinoma	1
	Depression of erythroid elements; patient had positive LE prep.	1
Confirm aspiration results	Diffuse infiltration wih eosinophils; focal infiltration with lymphocytes and plasma cells. Patient had positive LE prep.	1
	Total cases	20

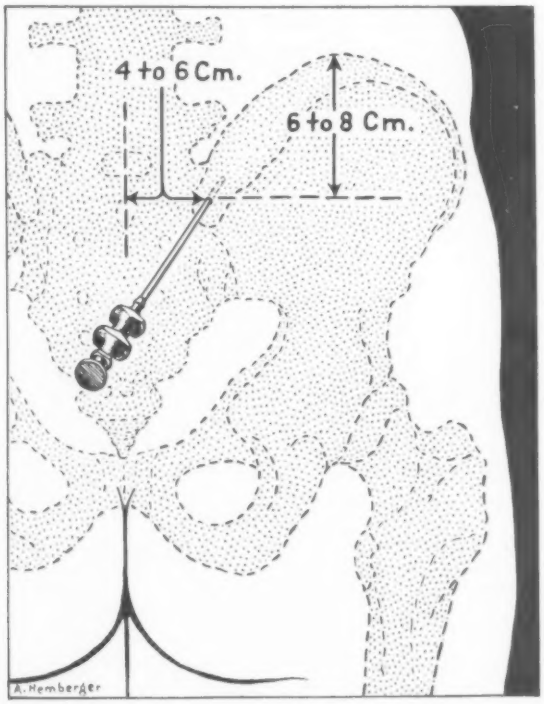

Fig. 1.—Schematic diagram of trephine needle in place. In most adults the position of the posterior superior iliac spine may be verified by using as a landmark the point of intersection of a vertical line drawn 4 to 6 cm. from the midline with a horizontal line drawn 6 to 8 cm. from the highest portion of the iliac crest. The needle is directed slightly superiorly and laterally as indicated.

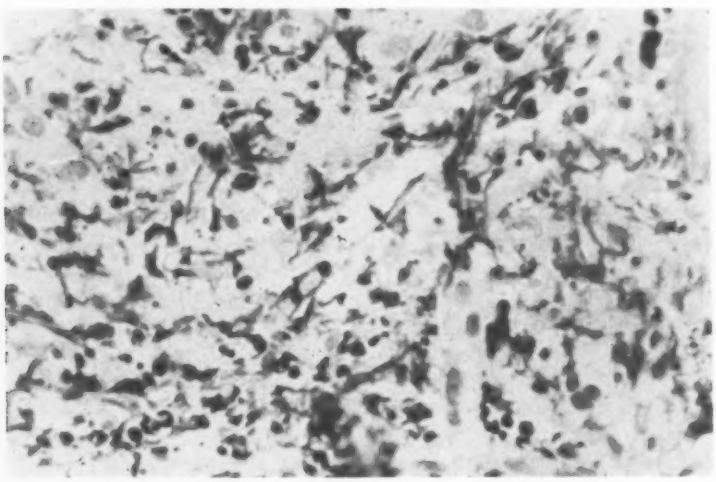

Fig. 2.—Bone marrow section showing myelofibrosis (× 120)

tions provided valuable additional information. The cells on the cover slips were in an excellent state of preservation and were as easily identified as those seen on aspiration smears. Perhaps the most important information obtained from the touch preparation was that relating to the cellularity of the preparations. If very few cells were seen on the touch preparation the section almost invariably showed a hypoplastic or aplastic bone marrow. It was possible, therefore, to make a presumptive diagnosis of marrow hypoplasia or myelofibrosis as soon as the touch preparations were stained, even before the bone marrow sections were returned from the histology laboratory.

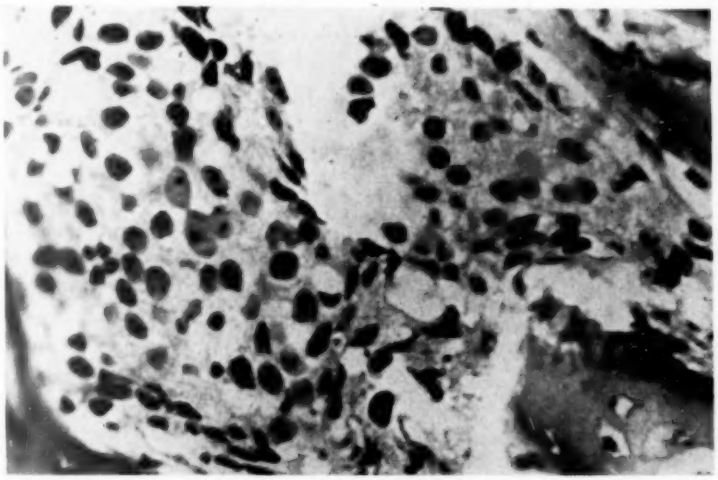

Fig. 3.—Bone marrow section showing tumor cells with dark staining nucleoli (× 400).

Discussion. The principal indication for doing a bone marrow biopsy is that of having obtained an inadequate sample by means of bone marrow aspiration. This is conventionally called a "dry tap" (Weisberger[10]). The reasons for this may include myelofibrosis, infiltration with neoplastic cells or granulomata, fatty infiltration of the bone marrow, and inadequate technique. The resulting "dry tap" does not discriminate between these conditions, and it usually becomes necessary to perform a bone marrow biopsy. It is clearly recognized that examination of the bone marrow section holds considerable advantage over the aspiration smear for the differentiation between neoplastic and granulomatous marrow infiltration (Dameshek, Henstell and Valentine[3]). Not infrequently, it is possible to obtain a micro-biopsy of an area infiltrated with tumor with this technique, whereas needle aspiration often is unsuccessful. Bone marrow biopsy also may be used in instances where it is suspected that aspirated material is not a representative sample of the bone marrow (Young and Osgood[11]). For example, a patient with a pancytopenia may show a very hyperplastic bone marrow aspiration, and yet by section it becomes apparent that the aspirated material represents only a small cellular focus in an almost totally aplastic bone marrow.

A number of other techniques have been devised in order to obtain a bone

marrow biopsy specimen. These include the use of special needles (Reddy[6], Turkel and Bethell[9]), miniature drills with a brace and bit (Favorite[4]), and surgical intervention or surgical trephine operation (Dameshek[2]), in order to obtain an adequate specimen. Some of these techniques require the use of the operating room and general anesthesia, the movement of critically ill patients, and the learning of special procedures which may be difficult, time-consuming and unreliable. The use of the modified Vim-Silverman needle technique for bone marrow biopsy may be done at the bedside without elaborate equipment, and with a minimum of discomfort to the patient. The procedure is well tolerated by patients who are toxic and critically ill.

When a "dry tap" or scanty bone marrow has been obtained with the aspiration technique, the probability is that some advanced pathologic changes have occurred in the bone marrow. In only 2 of the 20 patients studied was it found that faulty technique was responsible for the hypocellular preparations. If a second bone marrow aspiration again is inadequate for diagnosis it is suggested that the Vim-Silverman bone marrow biopsy be the next step.

The posterior superior iliac spine probably is the best available bone marrow biopsy site. With the patient in the prone position, he is comfortable and unable to observe the procedure. The site of entry is easy to locate, and the possibility of injury to important soft tissue structures is remote. The distance between periosteal surfaces is about 4 cm. and the actual medullary space is about 3 cm. in cross section in most adults. The cutting blade is advanced a distance of less than 1 cm. into the marrow space, and it is unlikely that it could be forced through the opposing cortical bone.

The actual histologic technique employed in handling the biopsy specimen is of considerable importance. Decalcification of the bone marrow biopsy specimen has aided immeasurably in obtaining good histologic material. Without decalcification the marrow specimen often becomes fragmented and poorly stained. In addition, it is difficult to keep the cutting edge of the microtome blade sharp. It also is possible to stain the bone marrow sections for iron for the purpose of semi-quantitating marrow hemosiderin. The touch preparation should be made on chemically clean cover slips, devoid of both fat and particulate material. The biopsy specimen must only be "touched" to the cover slip and not pulled across the glass. The latter procedure seems to distort the cells to a considerable extent and makes their subsequent identification unreliable.

Summary. The results obtained with a bedside Vim-Silverman bone marrow biopsy technique on 20 patients are reported. The method has been found particularly useful in instances where bone marrow sampling has been inadequate by means of aspiration. The method is recommended as being simple, safe, convenient to the patient, and entirely adequate for diagnosis. It is believed that this method will supplant the use of a surgical trephine procedure for biopsy of the bone marrow in most instances.

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SUMMARIO IN INTERLINGUA

Biopsia Medullar a Agulia

Es reportate le resultatos obtenite in le uso de un methodo de biopsia a agulia Vim-Silverman pro colliger specimens de medulla ossee sin mover le patiente. Datos ab 20 casos es includite. Le methodo se ha provate specialmente utile in casos in que le specimens de medulla ossee obtenite per aspiration esseva inadequate. Le methodo es recommendate como simple, salve, disproviste de disconforto pro le patiente, e completemente adequate pro le diagnose. Es exprimite le opinion que iste methodo va reimplaciar le chirurgia a trephina pro biopsia de medulla ossee in le majoritate del casos.

SUMMARIO IN INTERLINGUA

(See page 174 for original article)

Effectos Cardiovascular de Hydrochloruro Phenyl-1-Butyl-Norsuprifenic (Arlidina)

1. Arlidina per via parenteral augmenta le rendimento cardiac per un valor medie de 34% e reduce le resistentia peripheric per 23%.

2. Le droga augmenta le fluxo de sanguine a in le sura per approximativemente 30%, sed certe patientes ha augmentos transitori que es multo plus marcate. Le fluxo de sanguine in le pelle non es afficite. Le augmento in le fluxo in le sura representa per consequente le plus probabilemente un augmento del alimentation sanguinee del musculo.

3. Nulle uniforme effecto del droga super le symptoma de claudication intermittente esseva notate in studios a trottoir rolante.

4. Le effectos super le frequentia cardiac e super le tension de sanguine esseva minimal, e nulle adverse effectos lateral esseva notate.

Le effectos cardiovascular de Arlidina esseva studiate per un varietate de differente methodos. Esseva trovate que le rendimento cardiac cresceva per un valor medie de 34% e que le resistentia peripheric decresceva per un valor medie de 23% post administrationes parenteral del droga. Le fluxos verso le pelle non esseva afficite. Tamen, le fluxo al sura cresceva per circa 30%. Nulle uniforme effecto super claudication intermittente esseva constatate in studios con le trottoir rolante. Nulle adverse effectos lateral esseva notate, e le effecto super le frequentia cardiac e super le tension del sanguine esseva minimal.

THE USE OF MECHANICAL ASSISTANCE IN TREATING CARDIOPULMONARY DISEASES

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Following the development of pressure breathing some 20 years ago (Barach, Martin and Eckman[1]), many reports have appeared of its use for the treatment of cardiopulmonary diseases, such as acute pulmonary edema, asthma, bronchitis, and emphysema (Gray and MacIver[3]). With particular reference to emphysema two problems have become apparent. First, mouth positive pressure alone tends to overdistend an already distended lung (Gray, Gray and Dillinger[2]) and second, the diaphragm is often so weak in these patients that between treatments ventilation is ineffective.

The first problem, overdistention, was dealt with by using a rhythmically inflated and deflated pneumatic belt covering the abdomen and lower rib cage. The belt* cycles synchronously with the expiratory phase of an automatically cycled inspiratory positive pressure breathing apparatus† activated by a power source which provides a cycle of 40% inspiration, 60% expiration. The second problem, an ineffective diaphragm, has been partially met by breathing exercises. For greater efficiency, an electronic neuromuscular stimulator with two applicators‡ was used. The stimulus of each applicator alternated with the other in a rhythmical manner at a selected rate and intensity. One applicator was applied to the epigastrium and the other over the lower abdominal wall. In one group of normal subjects only the diaphragmatic electrode was used. Electronically stimulated ventilation using somewhat different types of apparatus has been shown to be effective (Holmes *et al.*[4], Sarnoff, Hardenbergh and Whittenberger[5]).

The present study was aimed at determining the practicality of the two apparatuses and their immediate effect on ventilation. With this in mind acute studies were done in groups of normal subjects and patients with a variety of chronic respiratory difficulties. The therapeutic efficacy over a long period of time cannot be evaluated by this means and will be the object of a future study.

Material and Methods. The normal subjects consisted of medical students, research fellows, and members of the medical staff.

*Technicon-Huxley Pneumobelt manufactured by Conitech Ltd., Chauncey, N.Y.

†Technicon-Huxley Multilung manufactured by Conitech Ltd., Chauncey, N.Y.

‡Batronic Neuromuscular Stimulator, Model A, with 2 stimulator electrodes, manufactured by Batrow Laboratories, Inc., Branford, Conn.

TABLE 1.—RESULTS WITH PNEUMOBELT-IPPB.

Name	*Age*	*Diagnosis*	*Treatment*	*End-tidal CO_2 %*	*Tidal Volume ml.*	*Peak Velocity ml./sec. in*	*Peak Velocity ml./sec. out*
Ha	35	N. S.	Ambient	4.95	750	500	250
			Belt	4.50	1150	555	500
			Belt & IPPB	4.00	1850	600	350
Jo	35	N. S.	Ambient	4.95	240	250	250
			Belt	4.50	750	350	300
			Belt & IPPB	4.00	1000	350	400
Hi	40	N. S.	Ambient	4.20	750	370	370
			Belt	4.30	755	370	370
			Belt & IPPB	4.30	750	370	370
			Ambient	4.25	625	650	650
			IPPB	4.25	1000	1700	900
			Belt	4.00	1100	1350	1000
Fi	41	N. S.	Belt & IPPB	3.70	1550	2100	1550
			Ambient	4.59	450	500	300
			IPPB	4.25	800	1150	750
			Belt & IPPB	3.40	1000	1500	900
			Belt	3.40	725	850	850
			Ambient	5.15	600	700	400
			IPPB	4.25	1100	1800	1150
			Belt	3.95	1250	1500	1500
Gr	40	N. S.	Belt & IPPB	3.10	1800	2300	1800
			Ambient	4.80	450	600	400
			IPPB	4.25	900	1700	1250
			Belt	4.15	900	1000	1000
			Belt & IPPB	3.35	1750	2200	1500
Bu	40	N. S.	Ambient	4.50	800	600	500
			Belt	4.25	1050	1150	850
			Belt & IPPB	4.15	1200	1500	1250
Ma	70	Bronchiectasis	Ambient	5.75	300	400	250
			Belt	5.30	300	400	250
			Belt & IPPB	5.75	300	400	250
Me	68	Emphysema	Ambient	4.90	200	1300	200
			Belt	4.90	400	450	500
			Belt & IPPB	4.33	560	750	500
We	25	Post-polio	Belt	4.50	300	370	500
		resp. paralysis	Belt & IPPB	4.00	1200	850	850
			Ambient	4.20	120	250	300
Po		Bronchiectasis	Ambient	5.55	600	1450	1225
	54	Emphysema	Belt & IPPB	5.30	675	1450	1225
#1			Belt	5.55	840	1450	750
Po			Ambient	5.80	850	800	800
#2			Belt	5.80	950	850	400
			Belt & IPPB	5.80	2200	1250	1000
Si	35	Asthma	Ambient	3.85	625	875	350
			Belt	3.20	1145	1225	875
			Belt & IPPB	2.90	1330	1575	1050
Mi	50	Bronchitis	Ambient	3.80	510	500	180
		Emphysema	IPPB	3.50	835	750	360
			Belt	3.50	720	610	450
			Belt & IPPB	3.06	1000	970	450

N. S. = Normal Subject.
Po #1 and #2 = The same patient tested at one month interval.

The patients were drawn from the wards and the Cardiopulmonary Clinic of the Grace-New Haven Community Hospital. The Pneumobelt-IPPB equipment was tested on 6 normal subjects and 6 patients (one patient on two different occasions). Two patients were treated during the course of carbon dioxide narcosis and apnea, and 11 patients had the pneumobelt-IPPB apparatus substituted for conventional IPPB therapy. These patients are not included in Table 1 since spirometry was not done. The neuromuscular stimulator was used on 18 normal subjects and 6 patients, all of whom had spirometry recorded. Eight of the normal subjects had only the diaphragmatic stimulator applied.

Problems of method were somewhat different in evaluating the two apparatuses. In the case of the Pneumobelt-IPPB apparatus the relationship of the patient's inspiratory and expiratory phases to those of the apparatus was readily apparent, hence we were largely concerned with tidal volume and efficiency. In evaluating these the output of a pneumotachograph was recorded as air flow velocity and integrated as tidal volume on a multichannel recorder, and a continuous tracing of end-tidal carbon dioxide concentration determined by an infra-red carbon dioxide meter was recorded simultaneously. Thus, the effect of the apparatus on the air flow velocity during both inspiration (mouth positive pressure) and expiration (belt inflation)

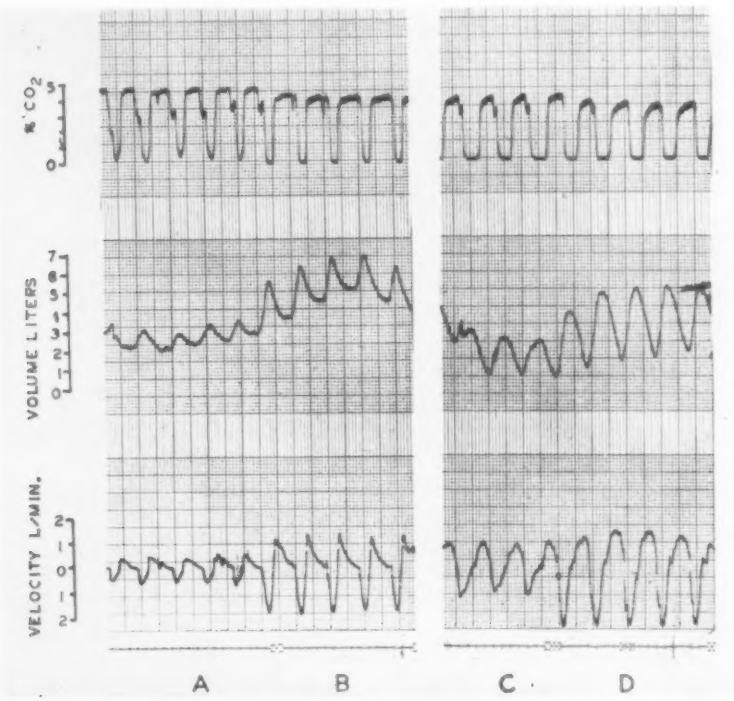

Fig. 1.—Effect of pneumobelt. Upper graph represents end-tidal CO_2 concentration; middle graph tidal volume (inspiration up, expiration down); lower graph airflow velocity (inspiration down, expiration up).

A. Ambient breathing.

B. Inspiratory positive pressure (I.P.P.B.) only. Note higher resting position on volume graph, higher tidal volume, lower CO_2 and higher inspiratory velocity. There is a high expiratory velocity spike related to elastic recoil.

C. Pneumobelt only. Note lower resting position, further reduction of CO_2, and broadening of the expiratory velocity curve.

D. Pneumobelt plus I.P.P.B. Note that all factors show improvement over any of the other graphs.

could be determined as well as the resulting tidal volume (Fig. 1). A rough estimate of alveolar ventilation as reflected by changes in end-tidal carbon dioxide concentration could also be made.

In evaluating the neuromuscular stimulator on the other hand it was necessary to establish that inspiration and expiration were actually in phase with the equipment since widespread muscular contractions incident to the stimulus made visual observation difficult and inaccurate. For this reason two additional channels were recorded simultaneously with the velocity and tidal volume channels on a 4-channel recorder. The first of these channels recorded the period of output of the diaphragmatic stimulator, the second that of the abdominal stimulator (Fig. 2). This record indicated whether or not inspiration and expiration coincided with the output of the respective electrodes. Very early it was found that erratic breathing occurring during the initial or adaptation phase of the neuromuscular stimulator always lowered the end-tidal carbon dioxide. The latter appeared to be of little value when the stimulator was used, and such data are not included in this part of the study.

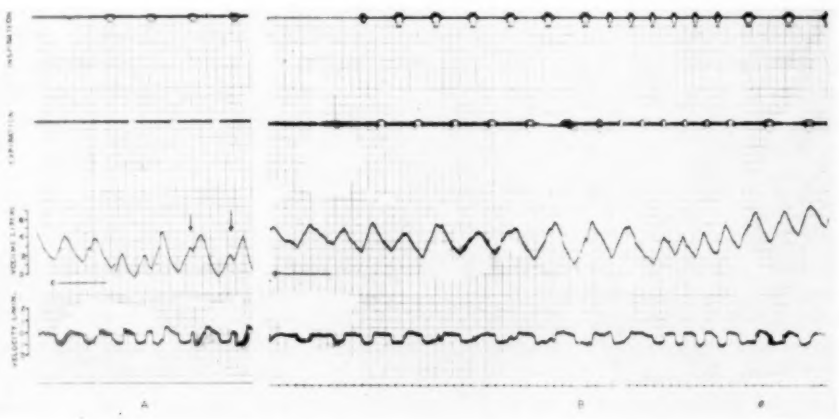

Fig. 2.—Effect of neuromuscular stimulator. Top graph shows a lozenge-shaped mark with inspiratory stimulus; next lower graph shows the same for expiratory stimulus. Volume and velocity graphs as in Fig. 1.

A. A subject who attempted to maintain his own rate. The vertical arrows show his own expiratory effort reversed by the inspiratory stimulus of the apparatus.

B. A subject who developed discordant but deep breathing on slow surge rate, but adapted to the apparatus at a higher rate. However, his tidal volume then dropped to ambient levels.

Results. I. "PNEUMOBELT" AND IPPB. An increased tidal volume was seen in all but 2 cases (Table 1). One of the patients (MA) and one normal subject (HI) failed to synchronize their breathing with the apparatus. Both belt and IPPB alone usually produced better ventilation than ambient breathing. Sometimes one was more effective than the other, but both together always proved better than either alone. In one patient (PO) IPPB seemed necessary for the patient to synchronize with automatic cycling. Improvement was reflected not only in tidal volume, but also in a lowering of the end-tidal carbon dioxide concentration, as well as increased velocity of air flow. The greater tidal volume led to increased velocity in both phases of respiration even when IPPB and the belt were used separately. In 2 of 13 patients not included in the Table the apparatus was used to provide total ventilation. These individuals had severe chronic bronchitis with emphysema, fibrosis and an alveolar-capillary block.

They entered the hospital in coma with near-apnea, hypoxia, and severe hypercapnia. In one case, because of great obesity, the patient could not be placed in a tank respirator, and mouth IPPB alone was insufficient to reverse the hypoventilation. When IPPB and Pneumobelt were applied his arterial carbon dioxide tension fell gradually and arterial oxygen saturation increased. The other patient, although in coma, fought the cycling of the respirator but had such ineffectual respiratory efforts of his own that he could not trigger demand type pressure ventilators. Morphine was given to depress his own respirations so that he would adjust to a tank-type respirator, but at this point vasomotor collapse developed. The abdominal belt was applied and not only provided adequate ventilation, but caused the patient's arterial blood pressure to rise toward normal. Whenever the pneumobelt function was interrupted, his blood pressure fell to shock levels, rising again upon resumption of belt breathing.

II. NEUROMUSCULAR STIMULATOR. In all of the 18 normal subjects there was an increased tidal volume when optimal rate was determined (Table 2). The velocity was variable, although usually increased. In cases in which velocity did not increase, tidal volume increased by virtue of a longer respiratory cycle. Two of the 18 subjects failed to synchronize with the machine, hence the increased tidal volume noted in these cases must have represented only hyperventilation associated with the experimental conditions. Proper placement of the diaphragmatic electrodes and determination of optimal rate were critical determinations often requiring considerable trial and error. Usually the subject would be out of phase with the stimulator for the first 3 or 4 breaths and then suddenly synchronize.

Generally, it was easier to obtain coordination in patients than in normal subjects. The patients allowed the stimulator to "take over" breathing rather quickly, but since this involved a change from primarily rib-cage breathing to primarily diaphragmatic and abdominal breathing, the net result was, in some cases, a lower tidal volume in contrast to the normal subjects all of whom showed increased tidal volume.

At the outset of the study, very large electrodes were used, and 2 of the patients (C.H. and C.R.) failed to respond even after prolonged trial. Later when a smaller diaphragmatic electrode was developed, both patients were retested and responded well (Table 2).

Discussion. Both types of equipment have provided adequate ventilation. Function studies were not done after the test, since little of a persisting nature could be expected from a single trial (Gray and MacIver[3]). The Pneumobelt-IPPB is simple to use and has ready patient acceptance. It appears to provide effective ventilation on single test use and over a period of several weeks 11 patients, not included in the Table, have indicated preference for the belt and IPPB over IPPB alone. Volume, velocity and carbon dioxide studies have not been done on the latter patients. The Pneumobelt-IPPB apparatus has been life-saving in 2 patients with chronic lung disease admitted because of asphyxia and demonstrating the depressed breathing of carbon dioxide narcosis.

With the Pneumobelt-IPPB combination, full inspiration is followed by a forced expiration in contrast to the passive expiration of IPPB alone. One would expect this to lower the dead space and increase alveolar ventilation. That such actually happens is suggested by the decrease in end-tidal

TABLE 2.—RESULTS WITH NEUROMUSCULAR STIMULATOR

Name	*Age*	*Diagnosis*	*Notes*	*Stimulator*		*Tidal volume ml.*	*Peak Velocity ml./sec.*	
				Diaghragm	*Abdominal*		*in*	*out*
Gr	40	N. S.		No	No	400	775	400
				Yes	No	650	1200	600
Us	35	N. S.		No	No	550	725	425
				Yes	No	575	850	425
Ba	40	N. S.		No	No	525	700	700
				Yes	No	675	1800	800
Ga	40	N. S.		No	No	360	475	325
				Yes	No	565	1500	800
Or	32	N. S.		No	No	565	750	450
				Yes	No	700	1025	1000
Cr	45	N. S.		No	No	475	625	425
				Yes	No	735	1975	975
Ab	30	N. S.		No	No	410	800	475
				Yes	No	550	1475	1450
Sa	35	N. S.		No	No	360	375	325
				Yes	No	615	1125	825
Th	22	N. S.		No	No	500	675	450
				Yes	Yes	500	900	900
Du	22	N. S.		No	No	500	1200	900
				Yes	Yes	1200	2100	2950
Sc	22	N. S.		No	No	550	1025	425
				Yes	Yes	850	950	950
Li	22	N. S.		No	No	710	825	925
				Yes	Yes	1220	1025	1125
Ar	21	N. S.		No	No	660	925	425
				Yes	Yes	815	1225	425
Wa	23	N. S.		No	No	375	650	425
			1	Yes	Yes	575	1025	650
			2	Yes	Yes	900	1025	650
Wal	22	N. S.		No	No	435	1225	650
				Yes	Yes	620	1225	925
Go	22	N. S.		No	No	575	825	425
				Yes	Yes	850	1225	1425
Sm	21	N. S.		No	No	560	575	550
				Yes	Yes	875	875	825
Pe	22	N. S.		No	No	290	600	300
				Yes	Yes	340	600	600
Ch	60	Bronchitis		No	No	1030	1200	700
		Emphysema		Yes	Yes	1180	1800	1000
Cr	58	Bronchitis		No	No	960	680	100
		Emphysema		Yes	Yes	670	380	280
Ca	64	Bronchitis		No	No	900	940	780
				Yes	Yes	440	800	460
Fe	68	Bronchitis		No	No	650	1150	550
				Yes	Yes	1450	2600	1050
Ha	60	Bronchitis		No	No	430	650	350
		Emphysema	3	Yes	Yes	890	850	850
			4	Yes	Yes	480	850	650
			5	No	No	480	725	650
Ti	50	Bronchitis		No	No	750	950	200
		Emphysema		Yes	Yes	950	1700	380

N. S. = normal subject.
1 = Rate normal for subject.
2 = Rate below normal for subject.
3 = Operator "counted" breaths for patient.
4 = Patient breathed without count.
5 = Resting after stimulator.

carbon dioxide found when the Pneumobelt was used. The neuromuscular stimulator required more attention to detail than the Pneumobelt and in normal subjects met some initial resistance, although patients seemed to accept it readily. Because of the critical nature of the electrode placement, it should only be used by personnel familiar with this type of neuromuscular stimulation, hence should probably be used in a Physical Medicine Department.

The mechanism whereby the neuromuscular stimulator brings about diaphragmatic contraction is not clear. The placement in the epigastrium suggests a focus of sensitive nerve endings, although local spread to neuromuscular junctions is possible. It is probably not a gasping response to a noxious stimulus, since the sensitive area is so highly specific and circumscribed. On the other hand, these studies do not rule out a simple stimulus-learning type of reaction. The fact that the patients, being anxious "to please," did better than normal subjects may suggest the latter. The large amount of extramuscular contraction tends to obscure visual evidence of diaphragmatic contraction and one can be certain that the diaphragm is contracting only if the patient is placed under a fluoroscope or a simultaneous stimulator output is recorded on a pneumotachograph chart as in the present study. Thus the desired effect, training the diaphragm, might not be accomplished unless the therapist were well trained and observed the patient closely.

Of interest was a difference in the way the patient coordinated to the two machines. In the case of the Pneumobelt-IPPB he simply adapted his rate to the machine and allowed it to assist, but, in most cases, he felt that he was still actively breathing. In the case of the Batronic neuromuscular stimulator he seemed to cease all respiratory effort and allowed the apparatus to take over, with little or no intercostal breathing. The latter observation suggests that the neuromuscular stimulator has a place in retraining the diaphragm in cases of severe emphysema in which all active diaphragmatic motion has ceased.

Summary. 1. A rhythmically inflated abdominal belt functioning alternately with mouth inspiratory positive pressure has proved to be an effective method for ventilating patients with severe pulmonary emphysema. It helps reduce overdistention, lowers alveolar carbon dioxide tension, and maintains blood pressure in cases of vasomotor instability.

2. An apparatus providing alternate and rhythmic electric neuromuscular stimulation of the diaphragm and lower abdominal muscles also provides adequate ventilation in emphysematous patients. It shows promise as an instrument useful in initiating diaphragmatic breathing exercises in those patients whose disease has impaired diaphragmatic motion.

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(Interlingua on page 139)

INTERMITTENT POSITIVE PRESSURE BREATHING AN EVALUATION OF ITS USE IN AEROSOL THERAPY OF CHRONIC PULMONARY EMPHYSEMA

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Intermittent inspiratory positive pressure breathing (IPPB/I) combined with bronchodilator aerosol nebulization was first introduced for clinical use in the treatment of pulmonary disease in 1948 (Motley *et al.*[10], Motley Lang and Gordon[12]). Since that time the use of IPPB/I equipment for administering aerosols has gained wide popularity and many studies have been reported on the beneficial results of this type of therapy in treating acute and chronic pulmonary disease (Gordon *et al.*[2], Maloney, Derrick and Whittenberger[5], Miller, Cade and Cushing[9], Motley and Tomashefski[14], Noehren[15], Segal *et al.*[16], Smart, Davenport and Pearson[17], Theodos[18], Tomashefski and Tchen[19], Whittenberger[20]). Experience during the ensuing years has clarified the special role of IPPB/I in the management of certain phases of the treatment of pulmonary disease. It has proved lifesaving in treating patients with decompensated respiratory acidosis and in maintaining or assisting ventilation in the comatose patient with pulmonary disease. In our experience it has proven of special value in making nebulization possible and more effective in patients who could not cooperate because of an impaired state of consciousness or inability to ventilate properly. The equipment's capacity for delivering 100% oxygen at high flow rates, coupled with its physiological effects on the cardiopulmonary circulation, has been useful in treating some cases of pulmonary edema. The apparatus has been found to be valuable in preventing postoperative atelectasis and hypoventilation, especially in patients with chronic lung disease or those undergoing thoracic surgery.

In all the circumstances listed above, the addition of aerosols of bronchodilators and detergents was of important benefit, but the indispensable role of the physiological effects of intermittent positive pressure breathing was clear. However, in the routine management of the average case of chronic pulmonary emphysema where nebulization of various aerosols has been one of the mainstays of therapy, the additive value of IPPB/I has not been clearly established. Advantages listed for nebulizing aerosol medications with IPPB/I include more uniform alveolar aeration and thus better distribution of aerosol particularly to the poorly ventilated areas; a higher peak expiratory flow velocity than inspiratory, thus promoting expectoration; improved respiratory muscle tone due to the induced breathing exercises; and more adequate ventilation with no increase in effort (Gordon *et al.*[2], Motley, Lang and Gordon[12], Motley and Tomashefski[14], Theodos[18]).

Fowler, Helmholz and Miller[1], after comparing the short-term effects of isopropylarterenol aerosol with and without IPPB/I, concluded that no significant differences existed. In an extension of this study, Miller, Fowler and Helmholz[8] reconfirmed this obser-

vation. Studies by Wu *et al.*[21] indicated that bronchodilators administered with IPPB/I in patients with bronchopulmonary disease produced a greater and more prolonged improvement of ventilatory function than when administered from a simple pressure source. In patients without increased secretions, however, they concluded that no advantages were detected, provided proper breathing techniques were utilized.

Subsequently Leslie, Dantes and Rosove[4] as a result of their studies concurred with the above authors, and in addition noted rather poor correlation between objective measurements and the patient's subjective evaluation of IPPB/I.

In our experience IPPB/I apparatus has been demonstrated to be a convenient and effective means of nebulizing bronchodilators and detergent agents. However, in view of the above findings, the cost of the equipment, and the additional maintenance problems, further studies to establish its contribution to nebulization therapy were felt to be indicated.

In addition, many of the patients objected to this form of therapy despite careful training unless the nebulizing pressures were lowered to under 5 cm. of water. These patients preferred ordinary pressure nebulization techniques, claiming that fatigue and increased shortness of breath were produced by IPPB/I. Although harmful effects of utilizing IPPB/I with bronchodilator aerosols in patients with emphysema were not demonstrated by studies by Motley, Lang and Gordon[11], a deterioration in ventilatory function in some cases has been reported by Segal *et al.*[16]. Further studies along these lines were also felt to be indicated.

I. THE SHORT TERM EFFECT OF PRESSURE NEBULIZATION OF 1:200 ISOPROPYLARTERENOL WITH AND WITHOUT IPPB/I.

Material and Method. Twenty-nine veteran patients averaging 58 years of age with chronic diffuse pulmonary emphysema, varying in degree from mild to very severe, were used as subjects for the first part of the study. Diagnoses were based on clinical examination, Roentgen-ray, and ventilatory studies. The pulmonary diagnoses carried in addition to emphysema, which was of the diffuse obstructive type predominantly, included the following: chronic bronchitis, 23; bronchial asthma, 14; bronchiectasis, 3; idiopathic diffuse pulmonary fibrosis, 2; cystic disease of the lung, 2; inactive pulmonary tuberculosis, 1. Thirteen of the patients had cor pulmonale but were compensated at the time of this study.

Each patient served as his own control and the short term effects of nebulized isopropylarterenol administered with and without IPPB/I were compared to the baseline ventilatory studies which were obtained before each study. Maximum cooperation and understanding of the procedure were obtained by instructing each patient in advance of the study. Medications which could affect the ventilatory studies were proscribed for at least 6 hours preceding the study. The factors of exhaustion and fatigue were avoided by separating the two sets of studies by at least 6 hours and usually 24 hours. The method of nebulization used on the first evaluation was alternated to randomize the influence of therapy, training, and psychological factors of being treated with "new equipment." Baseline ventilatory studies including supine and erect vital capacities (VC), supine and erect three-second timed vital capacities (3-VC), and maximal breathing capacity studies (MBC) were obtained before each nebulization. The supine measurements were discontinued when comparison of the results in the first 11 studies indicated that the supine VC and 3-VC measurements reflected responses of isopropylarterenol that were similar to the erect measurements but only less in degree. The ventilatory measurements were all repeated 15 minutes after each nebulization had been completed. The 13-liter Collins Respirometer was utilized for all the above measurements.

The first 20 patients received two separate nebulizations of 12 minims of 1:200 isopropylarterenol by two methods. In the first method, IPPB/I apparatus was utilized with 15 cm. of water pressure with compressed air as the pressure source and the aerosol directed through a mouth-piece rather than a mask. In the second method, which represented the technique we had utilized in the past, pressure for nebulizing was obtained

by reversing a portable electric suction unit. A by-pass vent controlled by the patient was placed in the tube system so that air pressure was forced through the nebulizer only during inspiration. In this latter method, as previously recommended by W. F. Miller, the patients were instructed to exhale, to inhale deeply with the aerosol stream directed into the open mouth and then to pause (Miller[7]). In the next 9 patients identical studies were done except that oxygen was used as a pressure source, to see whether the higher degree of oxygenation achieved with IPPB/I/O_2 would alter the results. No appreciable differences were demonstrated in the degrees of improvement and the results of the entire 29 studies were tabulated together for analysis.

After completing the two methods of nebulization, each patient was asked whether he detected any greater improvement with one method or the other, and these data were compared with the objective ventilatory measurements.

Results. The individual baseline ventilatory measurements as revealed by the three parameters of VC, 3-VC and MBC were indicative that this group represented a fairly wide range of ventilatory impairment with varying degrees of bronchial obstruction. Despite considerable variation at times in a given individual baseline with a definite trend for this to be greater on the second phase of testing, randomizing of the method of aerosol nebulization compensated for this effect. This is shown in Table 1.

The mean per cent increase following isopropylarterenol nebulization with and without IPPB/I are shown in Table 2. It is clearly evident that the addition of IPPB/I to the nebulization of this bronchodilator had no significant effect in this group of patients. Examination of the gross data revealed that of the 174 measurements of ventilatory function made following isopropylarterenol nebulization, there was some improvement noted in 87.5% and no change or a decrease in 12.5%. In the latter group the incidence of decreases in ventilatory functions was as frequent following isopropylarterenol nebulization with IPPB/I as it was without IPPB/I.

TABLE 1.—COMPARISON OF MEAN BASELINE VENTILATORY MEASUREMENTS (29 PATIENTS)

	V.C.	*3-V.C.*	*M.B.C.*
Mean baseline and range preceding aerosol with IPPB/I	2550 ml. (1550–4680) 70.2%*	1920 ml. (1100–4320) 75.1%†	42.8 L. (22.2–102.5) 37.9%*
Mean baseline and range preceding aerosol without IPPB/I	2480 ml. (1500–4540) 69.1%*	1860 ml. (1050–4100) 73.3%†	43.6 L. (19.4–127) 37.9%*

*Mean percent of normal
†Mean percent of observed V.C.

In view of the heterogeneity of the group, however, it was felt that analyses of the data according to the degree of pulmonary disability might be more revealing. Figure 1 reveals the results of reassessing the data according to the following groups: MBC greater than 30% of normal; MBC less than 30% of normal; and patients whose pulmonary disease was complicated by cor pulmonale. Considerable differences in the mean degree of response to bronchodilators by the three groups were shown, but the effect of adding IPPB/I was again shown to be statistically insignificant. Speculation regarding the significance of the minor differences shown is not warranted and is apt to lead to faulty conclusions. Further breakdown of data according to the

degrees of impairment of VC and 3-VC revealed no additional information.

All 29 patients noted some improvement with nebulization, and 21 of these patients felt that they could detect a definite difference in the degree of improvement when the two methods of isopropylarterenol nebulization were compared. Nine felt that they had better results using the ordinary nebulization technique. The other 12 preferred nebulization with IPPB/I. The actual differences based on per cent change of the baseline in each of the three

TABLE 2.—SHORT TERM EFFECT OF IPPB/I ON ISOPROPYLARTERENOL NEBULIZATION IN 29 PATIENTS WITH CHRONIC DIFFUSE PULMONARY EMPHYSEMA

	Isopropylarterenol nebulization without IPPB/I (A)		*Isopropylarterenol nebulization with IPPB/I (B)*		*Comparison of Results (B–A)*	
	Mean per cent increase and standard error	*t*	*Mean per cent increase and standard error*	*t*	*Mean per cent change*	*t*
Vital Capacity	10.8 ± 2.0	5.4*	11.2 ± 2.3	4.7*	+0.4	.03
Timed Vital Capacity (3 sec.)	14.2 ± 1.9	7.4*	12.4 ± 2.1	5.8*	−1.8	.82
Maximum Breathing Capacity	20.6 ± 3.1	6.6*	21.0 ± 4.1	5.1*	+0.4	.71

*t of 2.9 = P>.005 for 28 df

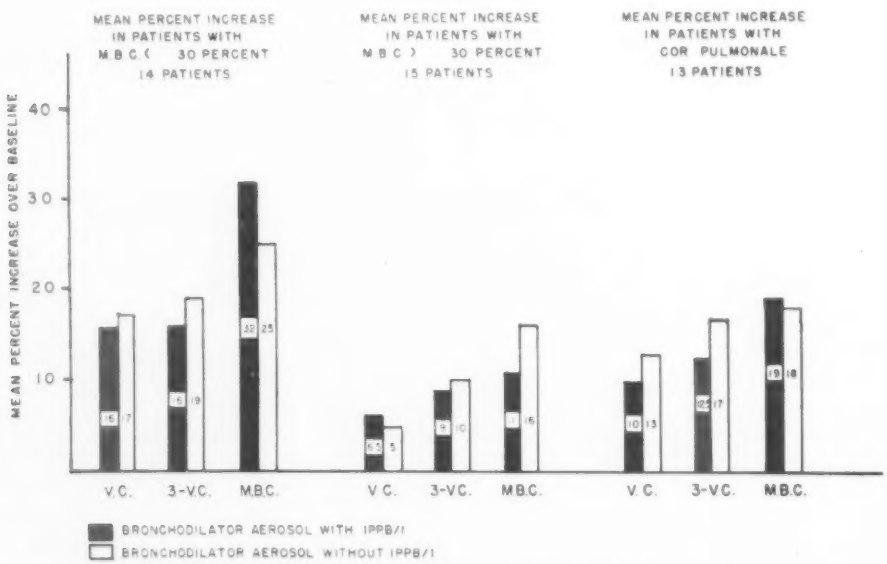

Fig. 1.—Effect of IPPB/I on bronchodilator nebulization in diffuse pulmonary emphysema (29 patients)

parameters were compared in these 21 individuals with the choice that they had made. These differences, although not statistically significant for the group, did show considerable differences in certain individuals but not in all parameters at the same time. Two of the three parameters measured showed an actual greater degree of increase with IPPB/I in only 5 of the 12 individuals preferring IPPB/I nebulization. Using these same criteria only 5 of the 9 who preferred ordinary pressure nebulization showed a greater response with that method. By these criteria as well as by gross inspection, it was apparent that patient choice was usually a reflection of factors other than actual difference in degree of improvement as was noted by Leslie, Dantes and Rosove[4].

II. THE EFFECT OF IPPB/I BY ITSELF ON THE VENTILATORY FUNCTION IN PATIENTS WITH CHRONIC DIFFUSE EMPHYSEMA.

Material and Method. A subsequent group of 25 male patients with an average age of 62 years with mild to severe degrees of chronic diffuse obstructive emphysema was tested. The mean vital capacity, three-second vital capacity, and maximum breathing capacity were comparable to the previous group (Table 3). Clinical diagnoses included chronic bronchial asthma, 10; chronic bronchitis, 15; bronchiectasis, 2; and cor pulmonale, 6.

The studies done were identical with those in the first group except that compressed air was used as the pressure source in all instances and the nebulized material was a placebo consisting of the 0.5% chlorotone base solution used for dissolving isopropylarterenol. The technician was informed that a new bronchodilator was being tested. In essence, the changes in the ventilatory baseline following IPPB/I/Air were compared to those in which IPPB/I was not utilized. This type of control was felt to be necessary as was shown later because of the rather wide fluctuations in baseline and changes induced by training, fatigue and certain psychological factors as noted in the first study.

Results. The mean per cent change from the baseline following IPPB/I therapy alone was insignificant in all three parameters as shown in Table 3, showing neither good nor harmful effects. However, inspection of individual responses reveals some rather distinct changes which could only be explained by findings of the control group. The control study which included nebulization of placebo without the use of IPPB/I revealed as expected a mean per cent change from the baseline which was insignificant statistically. However, here too, inspection of individual responses revealed rather wide ranges of response as with the former group. In the latter group this could only represent the human variables such as the effects of training, psychological effects of receiving a "new" medication, fatigue, and the varying degrees of encouragement given by the technician. For example, patient E.B., with a severe ventilatory defect, showed a 39.9% increase in MBC following IPPB/I, but also showed a 44.4% increase when the same placebo was nebulized without IPPB/I; clearly in this patient an indication of a fairly powerful psychological effect. On the other hand, some patients showed decreases in MBC of as much as 20% following placebo nebulization without IPPB/I, which must have reflected simple fatigue just as the result of repeating the ventilatory studies. This emphasizes again why any single ventilatory measurement to any form of treatment must be interpreted with caution.

As with the first study this material was reanalyzed according to the following groups: MBC greater than 30%; MBC less than 30%; and those individuals in whom cor pulmonale was present. Again, no significant differences were noted.

Discussion. The results of these ventilatory studies clearly indicate that IPPB/I does not enhance the effec-

TABLE 3.—SHORT TERM EFFECT OF IPPB AIR ALONE ON VENTILATORY FUNCTION IN 25 PATIENTS WITH CHRONIC DIFFUSE PULMONARY EMPHYSEMA

	Baseline			*Following Placebo Aerosol*		
	Mean V.C. per cent of normal	*Mean 3-V.C. per cent of Baseline*	*Mean M.B.C. per cent of normal*	*Mean per cent change V.C.*	*Mean per cent change 3-V.C.*	*Mean per cent change M.B.C.*
Placebo nebulization without IPPB/T	80.2 (40.3–126)	73.9 (55.9–92.6)	37.3 (15.4–86.9)	+1.3 (−9.3 to +30)	+0.2 (−10.5 to +7.9)	+5.0 (−10 to +44)
Placebo nebulization with IPPB/T	79.8 (50–122.9)	73.6 (58.3–92)	37.1 (17.1–81.7)	+0.4 (−14.6 to +12.5)	+1.9 (−11.3 to +27.8)	+5.6 (−6.1 to +39)

Figures in brackets represent range

tiveness of the pressure nebulized bronchodilator in the usual case of chronic diffuse obstructive pulmonary emphysema requiring such therapy. These findings are in agreement with other studies in which similar conclusions were made (Fowler, Helmholz and Miller[1], Leslie, Dantes and Rosove[4], Miller, Fowler and Helmholz[8], and Wu *et al.*[21]).

The second phase of this study revealed that IPPB/I even when utilized without oxygen or a bronchodilator had no apparent harmful effects in this group of patients as measured by changes in ventilatory function. This is in agreement with studies of Motley, Lang, and Gordon[11], who also demonstrated that there was no increase in the degree of emphysema as measured by residual volume even after prolonged use of IPPB/I. Segal's findings that IPPB/I alone caused a decrease in 60% of the determinations of MBC and 80% of VC are of interest (Segal *et al.*[16]). An average decrease in MBC of 1.5 L. per minute in the asthmatic, 0.5 L. per minute in the patient with emphysema, and 12.4 L. per minute in the patient with bronchiectasis should not be considered as statistically significant, at least in his first two groups. Some of his findings may be a reflection of the type of controls utilized and failure to take into consideration that changes in the ventilatory measurements may indicate human variables rather than the effect of therapy.

However, there are other potentially harmful effects of IPPB/I which must be considered. One would assume in observing some patients receiving IPPB/I therapy that their discomfort, whether due to poor coordination or other factors, must represent increased work and greater oxygen utilization. Closer analysis of Motley's data on arterial oxygen saturation following IPPB/I/Air/Bronchodilator revealed that nearly all showed an increase in oxygen saturation but there were several patients in whom a decrease occurred (Motley, Lang and Gordon[13]). Preliminary studies in our laboratory on changes in the arterial blood gases following IPPB/I/Air with and without bronchodilators revealed similar findings. Of 23 arterial gas studies three revealed decreases in oxygen saturation. This finding would suggest that IPPB/I had created an increased oxygen need which was not met by the improvement produced by the increased ventilation. Recent studies by Jones *et al.*[3], suggesting that under certain circumstances IPPB/I increases the work of breathing and diminishes alveolar ventilation, would also tend to confirm this impression.

Other untoward effects can be expected if IPPB/I is utilized for aerosol nebulization in the presence of pneumothorax, recent pulmonary hemorrhage, or where peripheral vascular collapse is imminent or has occurred (Gordon *et al.*[2], Maloney *et al.*[6], Motley, Lang and Gordon[12], and Theodos[18]).

The preceding discussion is not intended to deprecate IPPB/I therapy, for its unique role in managing certain phases of pulmonary disorders is fairly clearly defined and well established as previously discussed. It does stress the need for individualizing the type of pulmonary therapy for each case. It is also apparent that pressure nebulization of bronchodilators can be undertaken just as effectively without IPPB/I apparatus in the usual case of chronic pulmonary disease and that although IPPB/I is generally safe, a few contraindications do exist.

From a practical standpoint our experience with IPPB/I apparatus* is that these ingeniously devised units

*Ventalung. J. J. Monaghan Co., Denver, Colorado.
Bennett Valve TV-2P. J. Ray Bennett and Assoc., Inc., Los Angeles, Calif.

and especially the later models with intermittent nebulizing attachments have significant advantages making them extremely useful even for routine aerosol therapy. This was the result of taking advantage of our previously noted findings and keeping the hazards listed in mind. We found that by keeping mask pressure below 5 cm. of water, except when specifically indicated, the IPPB/I apparatus actually became a more convenient method for nebulizing aerosols, and required less supervision than did other pressure nebulizing methods. Three to 5 cm. of water pressure were used instead of zero pressure because this eliminated a small negative early inspiratory phase occasionally shown on actual measurement of mask pressures. This also largely avoided the known hazards of IPPB/I therapy and eliminated many of the complaints of increased shortness of breath and fatigue. Oxygen was used as the pressure source and the relief of anoxia, although temporary, contributed to the effectiveness of therapy. It is also an added safety factor, for bronchodilators do have potent cardiovascular effects and most patients under therapy are in the age range where coronary arteriosclerosis is common. A saving of both aerosol and oxygen are additional advantages worth noting.

Summary. The use of IPPB/I apparatus for administering aerosols in treating chronic pulmonary disease has gained considerable support since its introduction in 1948. Since then the unique value of the physiological effects of IPPB/I itself has been more clearly established as in the treatment of respiratory acidosis, in making nebulization more effective in certain patients, and in managing medical and surgical problems of hypoventilation. The value of aerosol therapy has been well confirmed but the additive value of utilizing IPPB/I for routine nebulization has been questioned. In addition harmful effects have been reported.

The effects of pressure nebulized bronchodilators on ventilatory function administered with and without IPPB/I in 29 patients with pulmonary emphysema were studied. No significant differences in the degree of improvement were demonstrable. The patients' choices as to the most effective method could not be correlated with objective measurements.

In the second study, changes in ventilatory function following pressure nebulization of a placebo with and without IPPB/I were compared in 25 patients with pulmonary emphysema. No significant beneficial or harmful effects on ventilatory function attributable to IPPB/I were shown. Changes in ventilatory function due to psychological or other factors were frequently demonstrated in both studies.

Contraindications to IPPB/I are few and include recent pneumothorax, pulmonary hemorrhage, shock, and certain cases of decreased cardiovascular reserve. Preliminary studies in our laboratory have revealed decreases in oxygen saturation following IPPB/I/Air in a few patients.

From a practical standpoint the automatic and intermittent nebulizing features of IPPB/I which save O_2 and aerosol make this apparatus extremely useful. By using low mask pressure, except when specifically indicated and O_2 as the pressure source, this unit has proven to be safe, effective, and convenient for routine aerosol treatment. Emphasis, however, is placed on the need for individualizing treatment for each patient.

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AN EVALUATION OF THE ELECTROCARDIOGRAM AND THE ACIDITY OF THE URINE AS A SCREENING TEST FOR PRIMARY ALDOSTERONISM*

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Both hypertension and some degree of hypokalemia have been present in all cases of primary aldosteronism reported to date. In addition, the routine urinalysis frequently has revealed a low specific gravity and an alkaline reaction. In cases with significant diastolic hypertension, electrocardiograms frequently, if not usually, are part of the investigation; and abnormalities of the tracing may be the first clue that the patient has hypokalemia and possibly primary aldosteronism. A detailed study has been made of the electrocardiographic criteria for hypokalemia (Weaver[15]).

This communication is in three parts having to do with three aspects of the general problem of using the electrocardiogram and the acidity of the urine as a screening test for primary aldosteronism: (1) a review of the electrocardiographic criteria for hypokalemia as based upon analysis of electrocardiograms made in 850 cases on the same day a low serum potassium value was found; (2) a review of the electrocardiograms of 5 patients with primary aldosteronism (surgically verified) who were studied at the Mayo Clinic, and of the 8 published electrocardiograms of patients reported by other investigators to have primary aldosteronism; and (3) a review of the electrocardiograms made during the year 1955 from approximately 5700 patients with hypertension, and of a clinical follow-up carried out in 20 cases of this group in which the electrocardiographic abnormalities were particularly suggestive of hypokalemia and the urine was alkaline.

ELECTROCARDIOGRAMS MADE DURING HYPOKALEMIA. Amongst the first to draw attention to the characteristic electrocardiographic changes associated with hypokalemia was Tarail[14], who in 1948 described the low amplitude of the T waves associated with the prolonged electrical systole. In that same year Nadler, Bellet and Lanning[8] emphasized the prominence of the U wave and suggested a relationship between this afterpotential and potassium me-

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tabolism. In 1949, Ernstene and Proudfit[6] pointed out the differences between the increased length of electrical systole in hypokalemia and hypocalcemia, and while including both conditions as a cause of increase in the length of a QT interval, suggested that the U waves might be responsible for lengthening the QT interval in hypokalemia by fusion with the T waves. Further descriptions of electrocardiographic signs associated with hypokalemia were given by Bellet and associates[2] in 1950 and by Reynolds, Martin and Homann[9] in 1951, with discussions again pertaining to the nature of the prolongation of the QT interval and, in addition, emphasis on a few cases with T-wave inversion. In 1953, Surawicz and Lepeschkin[13] delineated the problem pertaining to the identification of QT and QU intervals, and using different methods for determining the QT interval found that no change occurred with lowering of the serum potassium. Surawicz, Bellet, and co-workers[12], in 1957, discussed in detail the criteria for the electrocardiographic diagnosis of hypokalemia, utilizing such factors as U-wave amplitudes, relationship between amplitudes of U waves and T waves, and ST-segment depression. In 1954, Schwartz, Levine, and Relman[11] had suggested the importance of the relative amplitudes of the T waves and U waves.

In our study, the electrocardiograms made on the same day that a low level of serum potassium had been found were selected by review of the records in the biochemistry laboratory. A list was made of those cases in which the serum potassium values were less than 4.0 mEq. per L. (a limit deliberately set high), and then the electrocardiographic files were examined to see whether electrocardiograms had been made.

The numerous causes for hypokalemia represented in this group could be separated into the pathophysiologic and the pharmacologic. In the pathophysiologic category are the renal tubular defects, syndromes of adrenocortical hyperfunction of the Cushing variety, nephritis of the potassium-losing type, abnormal losses of gastrointestinal secretions (particularly in the postoperative state), and bilateral ureterocolostomy when this was associated with hyperchloremic acidosis. In the pharmacologic category are those disturbances associated with the use of diuretics (mercurial diuretics to some extent formerly, and chlorothiazide [Diuril] to a greater extent in the past 2 years), corticosteroid therapy, potassium-binding resins, and cathartics used in excess. The hypokalemia associated with the treatment of diabetic acidosis deserves a special category.

From this study attempting to define qualitatively and quantitatively the hypokalemic electrocardiogram, cases were excluded for the following reasons: (1) unsteady clinical states such as those in diabetic acidosis, hemodialysis, and postoperative periods; (2) electrocardiographic evidence of myocardial ischemia and of ventricular conduction defects; (3) ventricular rates in excess of 100; and (4) digitalis or quinidine therapy.

Of the 850 cases considered, there remained 130 in which the serum potassium values once or more times had measured between 4.0 mEq. and 1.6 mEq. while the patients were considered to be in a relatively steady state, and these cases were studied in detail.

To summarize the findings briefly, the typical, if not pathognomonic, electrocardiographic signs of hypokalemia are demonstrable only when the serum potassium is decreased to approximately 2 mEq. per L. The electrocardiogram in such cases shows a pro-

longed, undulating afterpotential with depression of the ST segment, and often the pronounced and prolonged U wave fuses with the end of the T wave so as to defy precise definition of the two. Inverted T waves were present in lead II in 13% of the cases, and in V_3 in 11%. It has been pointed out that the T-wave change may persist while the serum potassium returns to normal with therapy. This has been observed in one patient with a gastroileal anastomosis who was studied at the clinic by Gross and Waugh[7], and similar electrocardiographic changes have been emphasized recently by von Buchem[3]. From the electrocardiographic records published and those we have observed in our own cases, the persistent change in the electrocardiogram is the T-wave abnormality, not that of the U wave; and this aberration lasting a week or more might be attributed to the actual structural defects in the myocardial cell known to occur in animals with prolonged potassium deficits.

The electrocardiographic changes with moderate hypokalemic states (serum potassium concentrations between 3.0 and 3.5 mEq.) are characteristic but not diagnostic, and are limited primarily to a prominent U wave; in our records the changes were best perceived in lead II and the midprecordial leads, V_2–V_4. It is not only the height, or the voltage, of the U wave but its relation to the voltage of the T wave which may render the electrocardiographic tracing characteristic of hypokalemia. In cases with normal blood pressure the prominence of the U wave in relation to the T wave may be even more strongly correlated with hypokalemia than in cases with hypertension, where a high U wave is an ordinary finding. In hypertensive cases the relation of U wave to T wave is of value; but in many such cases in which a prominent U wave suggests hypokalemia the serum potassium is found to be normal.

It is generally recognized that hypokalemic states are associated with alkalosis as a rule, and acidosis with hyperkalemic states; and Roberts and Magida[10] suggested that the electrocardiographic changes might be related to variation in the hydrogen-ion concentration rather than to variation of serum potassium. From limited clinical data it appears that the alkalotic state may potentiate the hypokalemic electrocardiographic aberration, while acidosis obscures the hypokalemic pattern. We have seen one patient with a serum potassium of 1.3 mEq. who was acidotic, in the postoperative state, and whose electrocardiogram was not characteristic of hypokalemia. The interpretation of the tracing was complicated by moderate tachycardia, however; and when this is present the development of a U wave may be obscured by the short diastolic period and the succeeding P wave.

The amplitude of the P wave may be slightly increased during the period of hypokalemia, and we have noted an incidence of atrial extrasystoles which is in excess of that occurring in ambulatory patients coming to the laboratory for electrocardiograms (Table 1).

The typical hypokalemic changes in the electrocardiogram may be seen in the tracing reproduced in Fig. 1 from the case of a young woman with the characterisic syndrome of primary aldosteronism and a serum potassium level of 1.8 mEq. per liter at the time the electrocardiogram was taken.

Of incidental interest is the past controversy regarding the length of the QT interval. In our own writings we have spoken often of the prolongation of the period of electrical activity. The work of Butcher and associates[4] suggested that early in hypokalemia

TABLE 1.—PERCENTAGE INCIDENCE OF EXTRASYSTOLES AMONG CONTROLS AND HYPOKALEMIC PATIENTS

	Control—1061 ambulant patients	*Hypokalemia ($K < 3.6$ mEq.; no drugs)*	
		51 normotensives	*51 hypertensives*
V.P.C.* only	8	8	8
A.P.C.† only	4	8	18
Both	1	8	4
Total V.P.C.	9	16	12
Total A.P.C.	5	16	22
Total both	13	24	30

*V.P.C. = ventricular premature contractions.
†A.P.C. = atrial premature contractions.

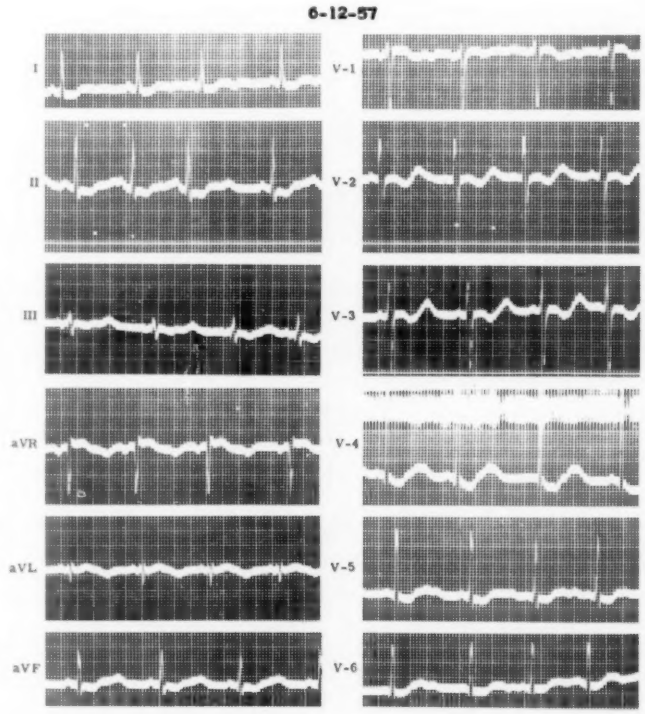

Fig. 1.—Woman 18 years old; proved primary aldosteronism; serum potassium 1.8 mEq. when above ECG obtained. Note bizarre undulating diastolic potentials representing fusion of T waves, U waves, and possibly positive afterpotentials. In some leads separate waves are seen, yet in V_2 the T–U fusion pattern might often be mislabeled as a diphasic T wave. The difficulty of QT measurement in such a tracing is obvious.

the QT interval might be slightly prolonged. Aside from the chance of assessing a U wave as a T wave, the difficulty in applying this idea relates to the practical impossibility in many instances of defining the end of the T wave *per se*, the presence of an additional afterpotential between the T wave and U wave, and the question

ELECTROCARDIOGRAMS IN PROVEN PRIMARY ALDOSTERONISM. Of the 5 cases of primary aldosteronism verified surgically at the clinic, 4 had electrocardiograms that would have been adequate to point to the hypokalemic state and suggest primary aldosteronism. In one case the electrocardiographic tracing was suggestive only. In Fig. 2 are re-

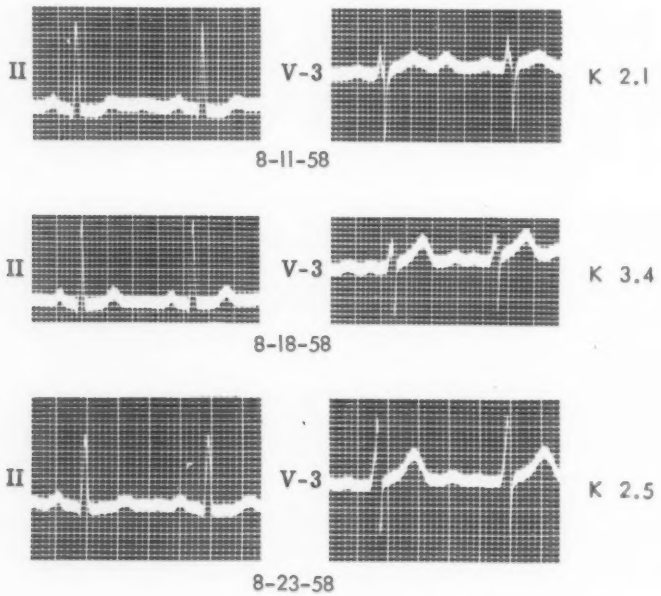

Fig. 2.—Man 20 years old; proved primary aldosteronism. The T-wave changes in lead II are classic, decreasing in amplitude as the potassium decreases. Also the T waves in V_3 (top record) are classic, having low amplitude with slow, slurred descent. The U waves in lead II are not abnormal, yet they disappear as potassium level increases. The U wave in V_3 (top record) is abnormally tall and equal in height to the T wave. The presence of the normal T–U complex in V_3 (bottom record) may be due to varied electrode position. Note slight lengthening of PR interval and slight ST-segment depression with hypokalemia. Note also the normal unchanging QT interval.

whether this is a bifid T wave or an independent wave; and to the range of QT intervals for normal persons with varying rates. Using available data we feel justified in concluding that the QT interval is slightly prolonged in many cases, or at least at the upper limits of normal, but certainly not grossly abnormal.

produced the electrocardiograms made on three occasions during a period of study on a young man who had severe hypertension, and the rather minimal changes in the electrocardiograms are noted. During metabolic studies the potassium concentration rose to a level near normal, and at this time the electrocardiogram became normal, al-

though the U wave still was rather prominent. At the time the potassium was 2.1 mEq. the U wave was very prominent in V_3, and in voltage equal to the T wave. The ST segment, T wave, and U wave in lead II are characteristic of hypokalemia also. In other cases the change may not be so dramatically portrayed.

first. The alkalinity of urine and perhaps some suppression of the maximal specific gravity of urine came next, and at this time the electrocardiogram was slightly suggestive of hypokalemia but would pass as normal. The hypertension progressed, the alkalinity and low specific gravity of the urine persisted, and hypokalemia was recorded;

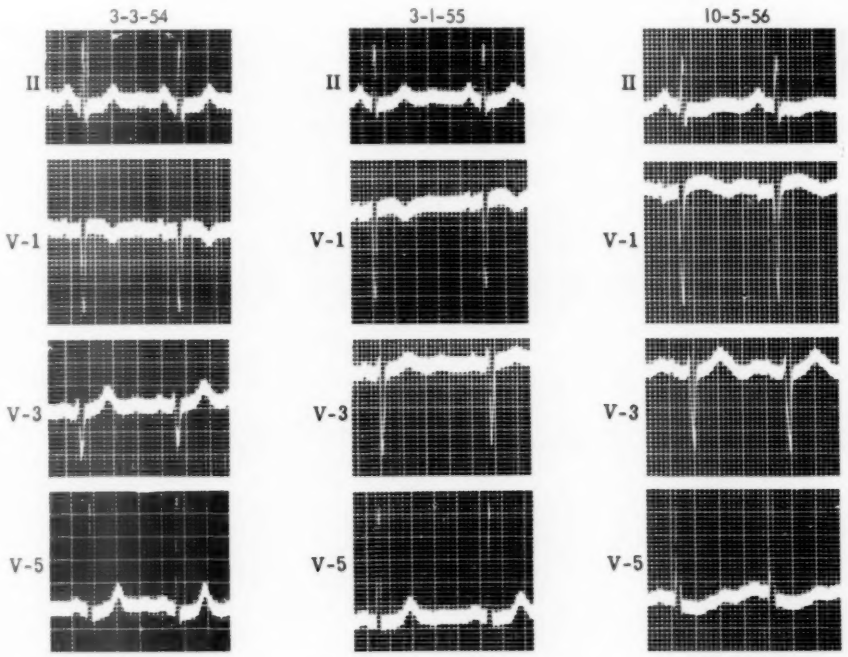

Fig. 3.—Woman 50 years old; proved primary aldosteronism. In lead II is noted a progressive lowering of the T wave concomitant with an increase in height of the U wave which finally fuses with the T. The same progressive changes are more apparent in V_3. Note the slow, slurred T-wave descent and the fusion of the U wave with the P wave in V_3 in the record of 10/5/56. Note also progressive ST-segment depression. Additional data in Table 2.

Two of the 5 patients with aldosteronism due to adrenal cortical tumors had been seen at the clinic over a period of years. The blood pressures and the results of routine urinalyses recorded in one case from the year 1942 until the present are given in Table 2. The sequence of events seems important. The hypertension appeared and the electrocardiogram (Fig. 3) became more characteristic. In 1957 the hypertension was observed to be severe, but following the removal of the 45-gm. adrenal cortical tumor the hypertension disappeared, the urine became acid, and the level of serum potassium returned to normal. Of some interest in this case is the fact

that the serum potassium concentration never reached the low level seen in other cases of primary aldosteronism.

The course of events in another case observed frequently at the clinic during 21 years is presented in Table 3. It may be noted that on the patient's third visit hypertension was recorded and the urine was reported acid. In 1951, the history was quite characteristic of hypokalemia, with weakness and symptoms suggesting tetany. There seemed no doubt that her state was markedly worsened by the use of chlorothiazide (Diuril) in 1957 and 1958, but whether she was more sensitive to this medication than other hypertensive patients cannot be stated with certainty. The electrocardiogram made in 1951 (Fig. 4) would be considered strongly supportive of the diagnosis of hypokalemia.

Among the reports of 32 cases of primary aldosteronism, the electrocardiograms from 8 have been published. All 8 are considered typical of hypo-

TABLE 2.—DATA FROM RECORD OF FEMALE PATIENT, AGED 34 YEARS IN 1942

Year	Blood pressure, mm. Hg	Urinalysis		Serum K, mEq./L.	Plasma CO_2, mEq./L.	Blood urea, mg./100 ml.	ECG evidence of hypokalemia
		Reaction	Specific gravity				
1942	140/88	acid	1.030	—	—	—	—
1949	140/90	acid	1.036	—	—	—	—
1951	155/90	acid	1.030	—	—	—	—
1953	190/100	acid	1.020	—	—	—	—
1954	192/100	alk.	1.018	—	—	24	suggestive
1955	190/100	alk.	1.010	3.2	29	30	supportive
		alk.	1.006	2.8	—	—	—
1956	195/110	alk.	1.005	—	—	—	—
		alk.	1.006	—	—	22	characteristic
1957	210/120	alk.	1.011	3.1	29	24	—
		alk.	1.010	3.2	—	—	—
11/25/57: operation—removal of adrenal cortical adenoma							
1958	140/85	acid	1.008	4.9	25	44	normal

TABLE 3—DATA FROM RECORD OF FEMALE PATIENT, AGED 37 YEARS IN 1937

Year	Blood pressure, mm. Hg	Urinalysis		Serum K, mEq./L.	Plasma CO_2, mEq./L.	Blood urea, mg./100 ml.	ECG evidence of hypokalemia
		Reaction	Specific gravity				
1937	120/80	alk.	1.015	—	—	—	—
1941	155/90	acid	1.019	—	—	—	—
1946	174/118	acid	1.010	—	—	—	normal
1948	184/90	alk.	1.011	—	—	20	suggestive
1949	220/106	alk.	1.010	—	—	32	suggestive
1951	196/90	alk.	1.003	—	—	28	characteristic
1952	220/90	alk.	1.008	—	—	34	characteristic
1953	244/100	alk.	1.006	—	—	32	characteristic
1954	196/114	acid	1.006	—	—	32	characteristic
1955	214/100	acid	1.002	—	—	—	characteristic
1956	195/85	alk.	1.005	—	—	42	characteristic
1958	210/90	alk.	1.004	3.3	34	38	characteristic

10/15/58: operation—removal of adrenal cortical adenoma. ECG aberration due to potassium loss, serum potassium concentration, and acid-base balance returned to normal on day following operation and have remained so. By the seventh postoperative day the blood pressure had fallen to normal values (130/70), and it has remained normal. The ECG continues to show left ventricular hypertrophy.

kalemia. Reports spoke of the electrocardiograms in 13 other cases as typical of or consistent with a hypokalemic state; the tracing in a fourteenth was said to be noncontributory. Reports of 10 cases did not mention electrocardiograms. In discussing the condition in the Endocrine Postgraduate Course in Syracuse, New York, in 1958, Conn[5] stated that he knew of more than 100 cases of primary aldosteronism, so the reports available in the literature represent only perhaps one quarter of the cases.

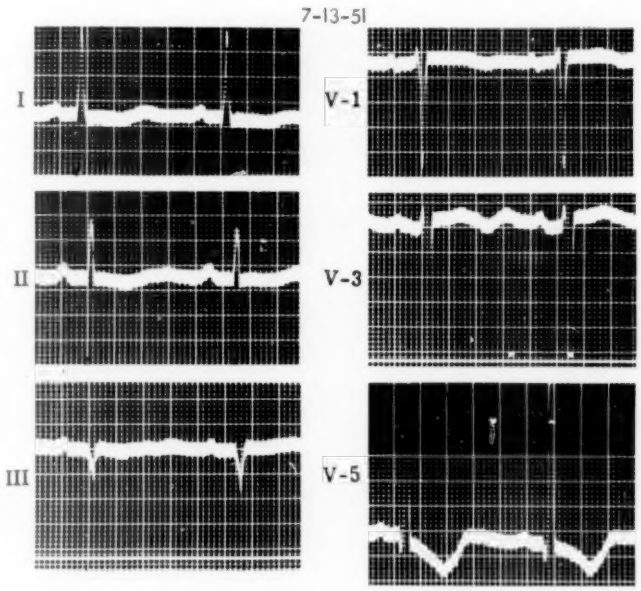

Fig. 4.—Woman 51 years old; proved primary aldosteronism. This tracing was selected during ECG screening for aldosteronism. In lead II note slight ST depression, slurred diphasic T fusing with an upright U wave. In V_3 note the characteristic low T wave with slow descent and the prominent U wave. Note also the slow ascent of the terminal portion of the T in V_5.

HYPERTENSION AND ELECTROCARDIOGRAPHIC EVIDENCE OF ALDOSTERONISM. The third part of our report deals with an attempt to find patients with primary aldosteronism among the hypertensive patients registering at the clinic in 1955 (Table 4). It may be noted that this year was prior to the time that chlorothiazide was used generally as a medication and that nearly all the patients were ambulatory. Of the total group of cases indexed as having hypertension, more than 5000 included electrocardiograms; but of these only 42 bore patterns suggestive of hypokalemia, and only approximately half of the 42 patients had alkaline urine. The clinical records of the 42 cases were studied in detail. Of the 7 patients known to be dead there were 2 whose histories contained features suggestive of primary aldosteronism. However, serum potassium values and necropsy data were not available to support the suspicion that these 2 patients might have had primary aldosteronism. Among the various clinical backgrounds associated with the abnormal

TABLE 4.—BACKGROUND AND FOLLOW-UP DATA IN CASES INDEXED AS HYPERTENSIVE IN 1955

Selection	*Cases*
Total indexed as hypertensive	7457
Cases with ECG	5717
ECG suggestive of hypokalemia	42
Alkaline urine	20

Follow-up	*Cases*
Excluding factors	
Associated genitourinary disease (with or without operation)	5
Established chronic renal disease	1
Medication with digitalis and quinidine	2
Recent status	
Doing well (normal serum potassium level in two)	4
Adrenal cortical tumor removed, 10/15/58 (now well)	1
Under surveillance (all have acid urine)	3
Known dead (no necropsy)	7
No follow-up	
Aged; severe complications	12
No contact (all had acid urine)	7
Total	42

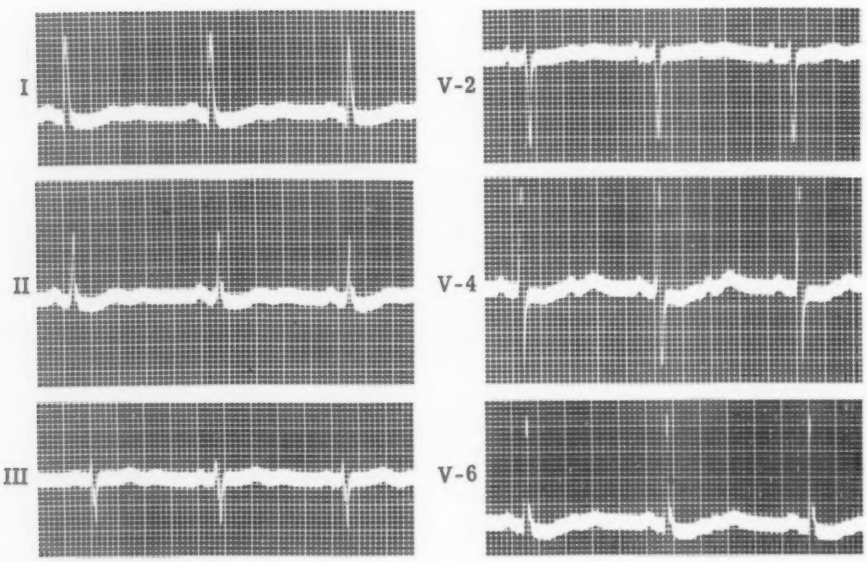

Fig. 5.—Woman 65 years old; essential hypertension (blood pressure 240/115 mm. Hg); serum potassium 4.3 mEq. when above ECG obtained. Note low T waves, tall U waves (reversal of normal ratio of T wave to U wave), T–U fusion, and ST-segment depression. Note multiple diastolic potentials in V_4 and V_6. These may represent notched T waves with U waves, or T waves and positive afterpotentials in addition to U waves. Note also the slightly prolonged QT interval.

electrocardiogram in the remaining 35 cases with or without proved hypokalemia, only one case was discovered in which the features were strongly suggestive. When this patient's record was requested for final analysis, it was found she had reregistered already because of weakness and congestive heart failure. Since then she has been proved to have primary aldosteroism.

our follow-up letter in 1958. The effect of digitalis and quinidine in causing electrocardiographic changes to mimic those of hypokalemia is illustrated in Fig. 7.

COMMENT. It is likely that in the fully developed syndrome of primary aldosteronism, hypokalemia is of such degree that characteristic alterations will appear in the electrocardiogram

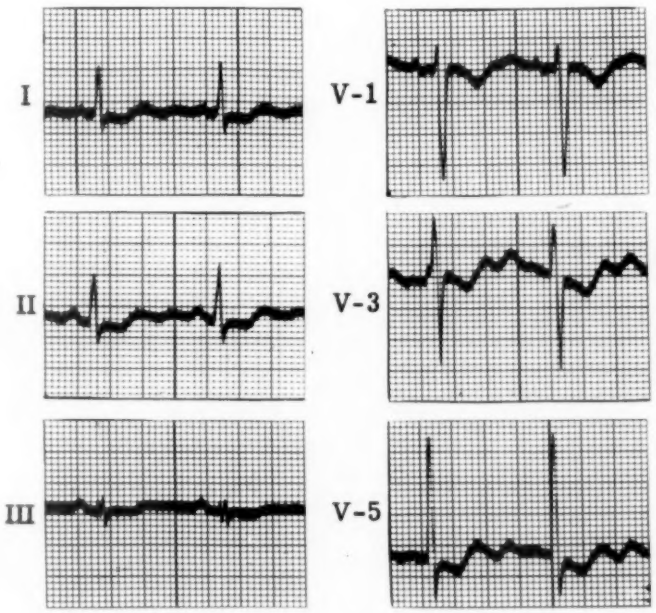

Fig. 6.—Woman 50 years old; essential hypertension. The above ECG was obtained in 1955, at which time there were no symptoms of electrolyte imbalance (blood pressure was 240/120 mm. Hg). In 1958 the serum potassium level was 4.0 mEq. Note diphasic T waves with abnormally tall U waves; also the ST-segment depression.

The electrocardiographic signs suggestive of hypokalemia that occurred in a hypertensive patient who had a normal serum potassium value are illustrated in Fig. 5. The electrocardiogram made in one case from the 1955 group of hypertensives (Fig. 6) was suggestive of hypokalemia; but the patient's home physician reported the potassium to be normal in response to

and should suggest the diagnosis. As a screening device the electrocardiogram cannot be claimed to be effective in the identification of early cases, and there are complicating interpretative ramifications; namely, that the prominent U wave taken as the hallmark of hypokalemia may be present in electrocardiograms of patients who are hypertensive but have normal serum

levels of potassium; that in patients with tachycardia the characteristic T–U configuration of hypokalemia may be obscured; and that in rare instances the electrocardiographic effects of digitalis and quinidine may simulate the hypokalemic pattern. According to our observations, the development of alkalinity and low specific gravity of urine, as well as electrocardiographic abnormalities suggesting hypokalemia, wherein the differential diagnosis lay between potassium-losing nephritis and primary aldosteronism, but at necropsy no structural change was found in either adrenals or kidneys.

Conclusions. This study suggests that in the course of primary aldosteronism the hypertension antedates the development of hypokalemia of sufficient degree to result in alkalinity and low specific gravity of urine and

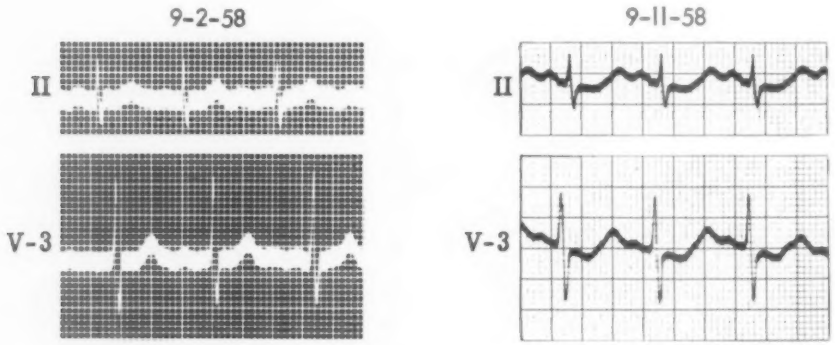

Fig. 7.—Woman 52 years old; idiopathic atrial fibrillation; cerebral emboli in recent past. Record at left shows atrial fibrillation not influenced by drugs; record at right shows ECG effects of digitoxin 0.1 mg. daily and quinidine sulfate 200 mg., four times daily. Note the prolonged slurred diastolic potential similar to that seen in Fig. 1.

follows the development of hypertension in patients with primary aldosteronism.

The diagnostic pitfalls are subtle, and as yet the means of differentiating primary aldosteronism in an early state from other conditions causing loss of potassium have not been defined accurately. The difficulty may be re-emphasized by mentioning the case report of Alsted and Halberg[1] (not included in the 32 reviewed above) the characteristic electrocardiographic abnormalities. Hence neither urinalysis nor electrocardiography can indicate primary aldosteronism in its early state, and at this time there is no simple screening test for the early case.

Also, we believe the incidence of the well-developed syndrome of primary aldosteronism with severe hypokalemia within a group of ambulatory hypertensive patients must be very low, probably not greater than 3 in 1000.

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SUMMARIO IN INTERLINGUA

Un Evalutation de Utilitate de Electrocardiogrammas e Determinationes del Aciditate Urinari in le Diagnose de Aldosteronismo Primari

Iste studio supporta le conclusion que in le curso de aldosteronismo primari le hypertension precede le disveloppamento de hypokaliemia de grados sufficiente pro causar alcalinitate e basse gravitate specific de urina e le anormalitates characteristic del electrocardiogramma. Per consequente, ni le analyse del urina ni le studio del electrocardiogramma pote indicar le presentia de aldosteronismo primari de stadio precoce. Al tempore presente il existe nulle simple test pro casos non-avantiate.

In plus, nos crede que le incidentia de ben-disveloppate aldosternismo primari con hypokaliemia sever inter patientes hypertensive ambulatori es multo basse. Probabilemente illo non excede 3 pro mille.

SOME CARDIOVASCULAR EFFECTS OF PHENYL-2-BUTYL-NORSUPRIFEN HYDROCHLORIDE (ARLIDIN)

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Most vasodilators, probably because of their predominant action on skin vessels, do little to alleviate the symptom of intermittent claudication. Recently, it has been claimed that Arlidin*, a synthetic drug belonging to the epinephrine-ephedrine group, is of value in patients with intermittent claudication (Murphy and Klasson[5], Pomeranze *et al.*[7], Stein[10]). The drug is alleged to have a threefold action: 1) specific dilatation of the blood vessels in skeletal muscle, 2) increase in cardiac output, and 3) increase in blood volume (Arlington-Funk Laboratories[1]). Since most of the physiological observations have been done in the experimental animal or are of a preliminary nature, it seemed of some value to study both the hemodynamics of the drug and its clinical usefulness in normal subjects and in patients with peripheral vascular disease.

Materials and Methods. CARDIAC OUTPUT. The effect of Arlidin on cardiac output was measured in 13 subjects. The ages and diagnoses are shown in Table 1. Only one of the subjects had evidence of organic heart disease and he was not in failure at the time of the study. Two patients had peripheral arteriosclerosis obliterans.

The subjects were studied 2 hours postprandially, without sedation, and after at least a 20-minute rest so that pulse and blood pressure became stable. After the control cardiac output had been performed, the patient was given 5 mg. of Arlidin subcutaneously and a repeat output was done in 20 to 30 minutes.

Cardiac outputs were performed by the dye dilution method of Hamilton and Stewart[4], using radioactive iodinated human serum albumin as the indicator. Cardiac output was calculated using the formula: COP in liter per minute $= \frac{I \times 60}{c \times t}$ where I = amount of iodinated serum albumin injected in counts per minute, c = mean concentration determined from the area of the curve, t = the time of the curve. Total peripheral resistance was calculated from the formula: TPR in dynes per cm. $^{-5}$ per second = mean blood pressure $\times \frac{1332}{COP}$ in ml. per second. The mean blood pressure was calculated from the formula: 1/3 the pulse pressure + the diastolic pressure.

PERIPHERAL CIRCULATION. Thirty-eight patients were subjects for the studies of the peripheral vascular effects of Arlidin. Seven of these were studied by two of the three

*Generously supplied by the U.S. Vitamin and Pharmaceutical Corporation.

TABLE 1.—EFFECT OF ARLIDIN ON CARDIAC OUTPUT AND PERIPHERAL RESISTANCE

Diagnosis and Age	*Control Output L./min.*	*Output After Arlidin*	*Increase %*	*Control Mean BP (mm. Hg)*	*Mean BP (mm. Hg) After Arlidin*	*Control Resistance dynes cm.$^{-5}$ sec.*	*Resistance After Arlidin dynes cm.$^{-5}$ sec.*	*Decrease %*
Cirrhosis (54)	7.40	11.80	59	—	—	—	—	—
Bronchiectasis (68)	6.52	7.98	22	81	93	980	930	5
Lymphoma (46)	7.48	7.95	6	—	—	—	—	—
Arteriosclerosis Obliterans (65)	4.95	8.14	60	—	—	—	—	—
Hypertension (39)	15.34	22.61	47	133	133	690	470	32
Carcinoma (57)	6.25	8.21	31	103	103	1319	1001	24
Fibrothorax (31)	9.67	13.92	44	97	87	803	499	38
Emphysema (61)	7.99	8.02	4	97	90	971	895	12
Mitral Stenosis (43)	4.37	5.89	35	98	91	1788	1237	31
Cirrhosis (66)	5.25	6.42	22	97	96	1468	1195	19
Arteriosclerosis Obliterans (77)	5.59	6.23	11	111	100	1589	1281	19
Normal (43)	7.30	12.36	70	97	84	1048	672	36
Normal (49)	6.89	9.27	34	81	93	938	799	15
Mean (53)	7.34	9.68	34	99	97	1159	898	23

methods employed and the remaining 31 were involved in only one test. There were 31 males and 7 females and the ages ranged from 45 to 70 years. Both toe and calf plethysmographic studies were conducted in a temperature-controlled room (21° C. ± 2° C.) with the patient lightly clad and lying comfortably on a cot.

Toe blood flows were determined by the method of Simeone *et al.*[9] in 11 patients. Of these, 6 had peripheral occlusive arterial disease as judged by ischemic symptoms, absent pulses, trophic skin changes, and the like. One patient had only venous disease, and 4 were without clinical evidences of cardiovascular disease. In a patient with Raynaud's disease, the same technique was applied to the determination of finger blood flows.

Venous occlusion plethysmography for the calf, using the technique previously described (Caliva *et al.*[2]), was performed in 23 patients, 13 of whom had arterial disease and 3 of whom had purely venous lesions. There were 7 normals.

In the plethysmographic studies, control blood flows were determined after the patient had been in the room for at least 30 minutes. When successive flows became fairly constant the patient was given 5 mg. of Arlidin subcutaneously. Blood flow determinations were then made at frequent intervals over the next 30 to 60 minutes. An average was made of all post-Arlidin flows with the exception of the first 5 minutes (the time of onset of drug effect [Riddell, Steel and McCoy[8]]). These were compared with the mean of the several contrc[1] flows.

Periodically during the entire procedure, brachial artery blood pressure was determined by auscultation. Heart rate was obtained from the records by pulse volume count.

THERAPEUTIC. A double blind study was conducted on 11 patients with arterial disease and symptoms of intermittent claudication who were exercised to the point of pain on a treadmill going at the rate of 2 miles per hour. At least 3 control determinations were made. The patients were then given tablets of either Arlidin "A" or "B" in doses ranging from 6 to 12 mg. four times daily. They were exercised under the same conditions every 2 weeks and the "A" and "B" preparations were interchanged. After completion of the entire study, it was learned that the "B" compound was the active one.

In some of the patients, prescriptions for Arlidin had been given by their physicians prior to being seen for this study but they were nevertheless admitted to the study and later given the unknown preparations. Individuals whose walking tolerance increased by 30 seconds were arbitrarily considered improved. Those in whom the tolerance decreased by the same amount were considered worse.

Results. HEART RATE AND BLOOD PRESSURE. No consistent effects on either heart rate or blood pressure were noted in any of the patients who received Arlidin (Table 1).

CARDIAC OUTPUT. The effects of Arlidin on cardiac output are shown in Table 1. It can be seen that there was a consistent rise in output with an increase in the mean from 7.34 to 9.68 liters per minute. This increase is statistically significant ($p<.01$) compared to previous studies done in normal subjects where the effect of time alone was studied (Table 2). In these control studies the mean change in two resting outputs done 20 minutes apart was a 5.6% decrease in output.

TABLE 2.—REPRODUCIBILITY OF THE DYE DILUTION METHOD FOR CARDIAC OUTPUT AT 20-MINUTE INTERVALS IN NORMAL SUBJECTS

	Cardiac Output 1 in L./min.	*Cardiac Output 2 in L./min.*
1	4 04	4 22
2	7 64	6 54
3	6 16	5 95
4	4 32	4 17
5	7 57	6 32
6	4 58	4 82
7	5 91	4 71
9	5 97	6 15
9	4 87	3 87
10	8 26	8 94
11	6 31	5 95
12	5 05	5 21
Mean	5 89	5 56 % change −5 6%
S.D. ±	0 56	

It should also be noted in Table 1 that with the increase in cardiac output, the calculated peripheral resistance fell from a mean of 1159 to 898 dynes cm.$^{-5}$ seconds.

TOE AND FINGER BLOOD FLOWS. Table 3 shows that parenteral Arlidin, in general, has little or no effect on the blood flow to the skin in either normal patients or in those with vascular disease. The one exception was a woman with advanced Raynaud's disease who had had bilateral cervical sympathectomies performed 8 years previously.

TABLE 3.—TOE BLOOD FLOW DETERMINATIONS

Diagnostic Group	*No. of Patients*	*Mean Blood Flow ml./100 ml./min. Control*	*Mean Blood Flows ml./100 ml./min. After Arlidin*	*Significant Change*
Venous disease (acute thrombophlebitis)	1	4 0	3 8	0
Normals	4	50	34	0
Raynaud's disease*	1	3 2	4 4	+38%
"Segmental" atherosclerosis	1	8	5	0
Arteriosclerosis obliterans	5	1 4	1 2	0

*Finger blood flows.

TABLE 4.—CALF BLOOD FLOW

Diagnostic Group	*No. of Patients*	*Mean Blood Flow ml./100 ml./min. Control*	*Mean Blood Flows ml./100 ml./min. After Arlidin*	*Significant Change*
Normals	7	2 1	2 8	+33%
Venous disease	3	3 1	4 3	+39%
Raynaud's disease	1	1 7	2 2	+29%
"Segmental" atherosclerosis	4	2 9	3 5	+21%
Arteriosclerosis obliterans	8	2 1	2 1	0

CALF FLOWS. Moderate increases in calf blood flow were recorded in most of the patients studied. As shown in Table 4, all of the groups investigated increased their calf flow between 20 and 40% with the exception of the patients with diffuse arterial disease. In this group of 8 patients, only 3 exhibited increases in flow after the drug. In both Tables 3 and 4, an average was taken of all post-Arlidin blood flows with the exception of above recorded in the first 5 minutes after drug administration.

In 20 of the 23 calf flow studies, there were one or two isolated determinations which were well above control levels. These increases were transitory and presumably marked peak drug effect. Figure 1 illustrates the data obtained in one such case.

THERAPEUTIC. No consistent effect on walking tolerance was demonstrated in any of our patients, regardless of which preparation they were taking. Six patients received known Arlidin tablets. Of these, one improved, 2 became worse, and 3 showed no change. Of 8 patients given preparation "A", 3 improved, 2 became worse, and 3 showed no change. With the "B" medication (the active preparation) 4 improved, one became worse and 6 showed no change.

Discussion. These studies would seem to confirm some of the previous work. Certainly the parenteral preparation of Arlidin significantly increases cardiac output. Since there was no alteration in pulse rate or blood pressure, this change represents an increased stroke volume and a decreased peripheral resistance. These results are

in agreement with those of Needleman and Horowitz who used a ballistocardiograph[6].

The peripheral vascular effects are also those that others have reported (Hensel, Ruef and Golenhofen[3], Stein[10], Walder[11]). However, we are in disagreement with Riddell, Steel and McCoy[8], who believe that the primary site of action is the skin vasculature transient increases occurred frequently. Walder[11] has made the same observation. It would seem that the time of peak drug action varies from patient to patient and that it is very short lived. We are unable to state from our data whether the increase in cardiac output is also a transient one and whether or not it occurs simultaneously with these peak calf flows.

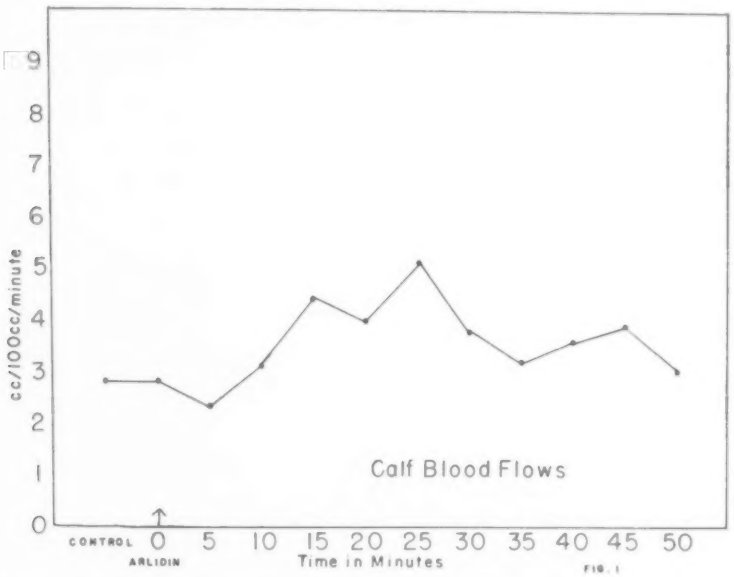

Fig. 1.—Graph showing the increase in calf blood flows after Arlidin in a patient with venous disease. Note transient peak effect.

since we were unable to show any significant rise in blood flow to the skin of the toe.

Blood flows as determined with a calf plethysmograph are representative of the circulation through both the skin and muscle of the calf. However, we believe that the increases recorded in these studies are indicative of a rise in muscle flow since the skin was shown to be unaffected in the toe studies.

The average increases in muscle flow were quite small, although larger but

The data in this series on the effect of the oral preparation in intermittent claudication are certainly unimpressive as far as beneficial effects are concerned. These, of course, should be interpreted with caution since the total number of patients is small and since the subjective element is so great in this symptom.

We are unable to state whether the primary drug action is to increase cardiac output or to dilate skeletal muscle vasculature or a combination of these

two. We are inclined to favor possibility number two and believe that the increase in cardiac output is secondary to a decrease in peripheral resistance. We are inclined to this belief since a primary increase in cardiac output without peripheral vasoconstriction should have resulted in increased skin flows which we did not record.

The clinical usefulness of the drug is doubtful. It is apparently safe in the absence of organic heart disease, but its peripheral vasodilating effects are minimal or very transient. Its practical value in intermittent claudication remains to be proven.

Conclusions. 1. Parenteral Arlidin increases cardiac output an average of 34% and decreases peripheral resistance by 23%.

2. The drug increases blood flow to the calf by approximately 30% although some patients have transient increases which are much higher. Skin blood flow is unaffected. The rise in calf flow, then, most probably represents increase in blood flow to the muscle.

3. No consistent drug effect on intermittent claudication was observed in treadmill studies.

4. Effects on heart rate and blood pressure were minimal, and no untoward effects were observed.

Summary. The cardiovascular effects of Arlidin were studied by a variety of different techniques. It was found that cardiac output increased an average of 34% and that peripheral resistance decreased 23% after parenteral administration. Blood flows to the skin were unaffected, although calf flows increased about 30%. No consistent drug effect on intermittent claudication was observed in a treadmill study. No untoward side effects were observed and the effects on heart rate and blood pressure were minimal.

ACKNOWLEDGMENTS The technical assistance of Miss Madeline Tuori, R.N. is acknowledged by the authors.

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(Interlingua on page 145)

PEUTZ-JEGHERS SYNDROME: FOLLOW-UPS ON PATIENTS REPORTED ON IN THE LITERATURE*

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Since 1949, when Jeghers, McKusick, and Katz[20] called attention to the diagnostic importance of an unusual familial disorder (previously described by and known as the syndrome of Peutz) and the publication in 1945 of an editorial in the Journal of the American Medical Association, there has been an awakening of interest in this syndrome. From the number of cases appearing in the literature thereafter, one can assume that it is not as rare a disease as was once thought.

Peutz-Jeghers syndrome is characterized by the deposition of melanin-pigmented spots in and about the lips and mouth and to a lesser degree in the skin, and by associated polyposis of the intestine. The polyps, which are usually observed in the small intestine, may cause obstruction and intussusception. They may also undergo malignant degeneration.

With the exception of the report by Jeghers, McKusick, and Katz[20], and a report by Dormandy[12] describing some 23 additional cases (and including full bibliography), the literature dealing with this syndrome has consisted primarily of case reports.

In an effort to assist in the consolidation of this widely scattered material, we previously published a review of the histopathologic aspects of this syndrome[41], based on material which we gathered from as many authors reporting in the literature as were willing or able to provide us with biopsy material, with the hope that intensive study of a larger body of material, all available for review at one time and by one group of investigators, might achieve a more comprehensive understanding of this syndrome.

Our observations on this material suggest that the intestinal polyps,

*The authors express their deepest appreciation to the following investigators: O. D. Fischer, R. M. T. Walker-Brash, A. K. Basu, E. P. Vary, M. A. Troxell, H. H. Wolff, A. Bruwer, W. P. Kleitsch, C. R. Savage, B. P. Perry, J. J. Zuska, H. Goldberg, P. Goldhaber, M. L. Bradford, S. C. Sommers, J. T. Freeman, I. R. Trimble, R. Andrew, E. Hinden, S. B. Berkowitz, S. B. Pearl, N. H. Shapiro, H. B. Young, and R. A. Weber. Without their generous cooperation and assistance this report would not have been possible.

whether in the stomach, small intestine, or colon, presented an essentially similar appearance: well differentiated but irregular glandular structures, producing moderate to abundant mucous secretion; that occasionally ulceration, hemorrhage, and nonspecific inflammation were manifest superficially; that no pigment was present in any polyps, even those of the colon; and that where malignant change was present, the growths still showed a benign adenomatous pattern, with carcinoma apparent only in deeper portions of the mucosa or in penetrating glands. It was thus possible to infer that malignant growth is likely to be well differentiated, slow to invade, and apt to remain localized. This assumption could only be strengthened by further study of this group of patients over a longer period.

Subsequently, these authors were again contacted by us[40] in order to obtain sufficient of their pictorial material to make possible the publication of an "atlas" of the oral lesions in this syndrome. This undertaking was prompted by the need to demonstrate the variety of pigmentations, areas, sites, sizes, and the like, which might all be considered pathognomonic of Peutz-Jeghers syndrome (when such pigmentation could be associated with symptoms of intestinal polyposis). It was hoped that full acquaintance by the professions with the appearance of oral and circumoral lesions might lead to the more frequent and prompt diagnosis of the syndrome, especially when associated with gastrointestinal polyp disease, as evidenced by periodic abdominal pain, unexplained anemia, and melena.

It was our opinion that primary importance should be placed on the natural course and history of the disease in a given individual. Much of this information was, of course, presented by the individual investigators in their case reports. However, except in those instances in which the syndrome terminated fatally before publication of the case report, a follow-up of lesions in these patients has been lost to the literature, especially since it has not been common practice for an investigator to report on his patient a second time except under unusual circumstances. We therefore felt that the publication of a follow-up on as many as possible of the patients for whom a follow-up report could be obtained would be desirable, since it would further and more critically delineate the course and natural history of the disease.

Accordingly, we again communicated with the authors of the increasing numbers of papers which had come to our attention in our search of the literature dealing with the Peutz-Jeghers syndrome and explained our wish to get a follow-up on each patient, requesting their cooperation in providing us with a summary of pertinent data from the time of publication until the present. Through the courtesy of these author-investigators, we are able to present herewith follow-up reports on 20 cases representing 19 diverse reports and follow-ups ranging from 1 year to 8 years post-publication.

Results. The data, together with the literature references from which previously reported details can be obtained, are presented in Table 1.

In addition, we have been provided with observations on 4 patients not previously reported on in the literature, and these histories are included herewith.

Of the 20 patients again reported on, the following summarization can be made: 7 of these patients have been lost to follow-up. One patient has died of metastatic carcinoma (associated with her polyposis) some 2 years after

TABLE 1.—SUMMARY OF FOLLOW-UP DATA ON PATIENTS WITH PEUTZ-JEGHERS SYNDROME.

Bibliography Reference (Published)	Reference—Current	Investigator	Patient No.	*Course Since Reporting*									*Current Status*						
				Died of malignancy associated with Peutz-Jeghers	Pain	Unexplained Anemia	Melena	Ulcers	Intussusception	Recurrence of intestinal difficulty	Further operation for intestinal symptoms	No follow-up possible	Living with no symptoms	Anemia	Increased pigmentation	Living with symptoms	Year of original report	Date of new report	No. years added by follow-up
13	14	Fischer, O. D.	1										x		x		51	2/57	6
33	34	Walker-Brash	2									x					54	—	—
4	5	Basu	3										x				52	1/58	6
31	32	Vary	4							x	4/56, 5/56		x				56	3/57	1
29	30	Troxell	5									x					54	—	—
36	37	Wolff	6									x				▶	52	—	—
11	10	Bruwer	7			x				x	4/56			x		x	54	7/57	3
3	19	Hinden	17		x				?	x						x	54	6/57	3

22	21	Kleitsch	8										x				55	2/58	3
25	26	Savage	9					x		x							x	54	9/57	3
23	24	Perry and Zuska*	10							x	6/54						x	50	6/55	5
17	18	Goldberg and Goldhaber	11									x						54	—	—
9	8	Bradford†	12				x			x	12/52, 3/53 6/58, 7/58						x	50	7/58	8+
27		Sommers	13									x						56	—	—
16	15	Freeman‡	14	x														55	57	2+
20	28	Trimble	15										x					49	8/57	8
1	2	Andrew	16									x						53	9/55	2
6	7	Berkowitz, Pearl, Shapiro	18		x					x	4/55	x						55	4/55	0+
38	39	Young	19 20		x					x			x x					56 54	57 3/58	1+ 4

* Total colectomy 6/54
† Total colectomy 3/53
‡ Metastic Ca originally observed

having been reported on in the literature. At the time of publication it was already known that the patient was suffering from metastatic carcinoma. No other patient is known to have developed a malignancy. Seven patients are living and free of intestinal symptoms. Eight patients have had recurrences of intestinal difficulties associated with Peutz-Jeghers syndrome, and 5 of these have required a total of 9 operations to relieve their difficulties. Of these 5 patients who were operated upon, one is now living and relatively well, 3 continue to have signs and symptoms, and one patient has been lost to follow-up.

In short: of 14 patients who were followed for varying periods, one has died of her disease, 8 have had intestinal recurrences, 5 have required surgical care, 5 are now troubled with the disease periodically, and 2 have had recurrences but are now relatively free of symptoms; while 7 are living and well.

The chronic but manageable course of this disease with good short-term prognosis and relatively low incidence of malignancy in adequately treated patients is further reaffirmed and strengthened.

There follow the reports on 4 additional patients described to us by those investigators with whom we have been in communication.

Case Reports. CASE 1. W.G., aged 20 years, had been hospitalized to permit a resection of part of the ilium for a polyp causing obstruction. Three months later he was operated upon for intestinal obstruction, about which there are no details.

He was again hospitalized in June, 1953, because of small bowel obstruction, and a resection and anastomosis were done. Subsequently, he was referred to the reporting physician who could add only the following: Race, apparently of English extraction; family history, not significant; past history: no vomiting, no indigestion, no bowel upset, no blood in the stool. For some years at intervals of weeks he has had attacks of lower abdominal pain lasting for a few hours or a few days, with intervals between attacks of one to many weeks; examination showed the usual pigmentation on the buccal mucosa, vermilion of the lips and sparse pigmentation on the face, hands, and arms. Sigmoidoscopy revealed numerous small, sessile polyps in the bowel and colon. Higher up there were a number of pedunculated polyps and, at 16 cm., a large cluster. One of these was removed for biopsy. The man was last seen on September 1, 1955, when he was symptom-free. (Presented through the courtesy of Dr. R. Andrew.)

CASE 2. B.G., was a 13-year-old Negro schoolgirl complaining of abdominal pain for 3 years. She had been seen previously for enuresis since birth, and on routine examination a microcytic hypochromic anemia was found. One of five stool specimens was guaiac positive. Her abdominal pain typically occurred at 3:00 p.m. to 5:00 p.m. and was relieved by sleeping for 30 minutes; there was occasional vomiting. She had a black sticky stool 7 days before admission. Family history and past history were negative. On examination she appeared small for her age and prepubertal.

Physical examination showed questionable clubbing of all fingers, telangiectasis of both sides of the nasal septum. The hemoglobin was 11.0 gm.%, hematocrit was 34. Radiographs showed a duodenal ulcer and spinal bifida occulta at L5. Polyposis of the duodenum, jejunum, and sigmoid colon was demonstrated by radiographic examination; polyps were seen by proctoscopy. Three large polyps were fulgurated. Twenty-six days later, a polyp of the duodenum was removed and the cecum, ascending, transverse, and descending colon was resected with ileosigmoid anastomosis. The pathologic diagnosis was multiple adenomatous polyps with superficial acute and chronic inflammation. The patient was discharged in good condition 17 days after the last operation.

Other members of the family were not examined. Although no specific observations as to perioral or digital pigmentation were recorded, and despite the fact that melanin pigmentation is a normal epithelial finding on the oral mucosa in Negroes, thus tending to obscure the typical picture, this case is being included since it was reported by the surgeon as Peutz-Jeghers syndrome. (Reported through the courtesy of Dr. S. C. Sommers.)

CASE 3. The patient whose case was reported by Kleitsch, Korn and Saichek[22] was,

as of February 21, 1958, in good health and has had no additional symptoms and no further operations. Kleitsch further reports, however, that the patient is the father of two boys ages 4 and 2½. The eldest son was examined when he was 18 months old and was found to be normal. The other boy, however, has polyposis and has had three polyps removed, apparently twice by way of laparotomy and once transrectally. This child is still having symptoms.

CASE 4. A brother of the patient reported on by Robert A. Weber[35] has been operated on by another surgeon for a small bowel polyp. This patient also has perioral pigmentation.

Summary. In order to study further Peutz-Jeghers syndrome, follow-ups on patients previously described in the literature as having oral melanin pigmentation with associated intestinal polyposis were sought from the physicians reporting them. The data so obtained provide a more comprehensive understanding of this syndrome, particularly as to its natural history, course, and prognosis in adequately treated patients.

Reports on 20 patients, of whom 14 could be followed for varying periods, were obtained from the reporting physicians, representing intervals ranging from one to 8 years following the publication of the case report.

Of 14 patients who could be followed, one has died of the disease, 8 have had recurrences, 5 have required surgical care, 5 are now troubled with the disease periodically, and 2 have had recurrences but are now relatively free of symptoms. Seven are living and well.

Through the courtesy of the cooperating physicians, 4 additional patients with this syndrome are reported.

The chronic but manageable course of this disease with good short-term prognosis and relatively low incidence of malignancy in adequately treated patients is further reaffirmed and strengthened.

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SUMMARIO IN INTERLINGUA

Syndrome de Peutz-Jeghers: Observationes Catamnestic in Patientes Reportate in Litteratura

Pro studiar additionalmente le syndrome de Peutz-Jeghers, reportos catamnestic relative a patientes previemente describite in le litteratura como habente oral pigmentation de melanina con associate polyposis intestinal esseva requestate ab le medicos qui habeva publicate ille descriptiones. Le datos obtenite in iste maniera provide un plus comprehensive intelligentia de iste syndrome, particularmente con respecto a su historia natural, su curso, e su prognose in casos recipiente un tractamento adequate.

Reportos pro 20 patientes, incluse 14 sub observation posttherapeutic durante varie periodos de temporte, esseva obtenite ab le medicos qui habeva tractate les. Le periodos de observation posttherapeutic in le varie casos variava inter un e octo annos.

Inter le 14 patientes pro qui reportos catamnestic esseva obtenite, un ha morite in consequentia del morbo, 8 ha habite recurrentias, 5 ha requirite un intervention chirurgic, 5 suffre ancora episodios periodic del morbo, e 2 ha cognoscite recurrentias sed se trova nunc relativemente libere de symptomas. Septe vive e se trova ben.

Gratias al cortesia del medicos responsabile, 4 casos additional del syndromes es reportate.

Es re-affirmate e corroborate le facto que le curso de iste morbo es non solmente chronic sed etiam tractabile e in plus que le prognose a curte vista pro casos del morbo es bon, durante que le incidentia de malignitate es relativemente basse in patientes subjicite a formas adequate de tractamento.

CLINICAL TRIALS WITH PHENETHYLDIGUANIDE IN SELECTED PATIENTS

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Phenethyldiguanide (DBI, Phenformin), has had clinical trials in a wide selection of diabetics by Krall[3,4], Odell[6], Pomeranze[7], Lambert[5], Skillman[8] and their co-workers. These workers have found DBI to be of use in 35 to 60% of unselected diabetics, with its greatest effectiveness in the mild adult onset diabetic who requires low doses of DBI. However, because of its higher incidence of side effects, DBI has not been as useful in the therapy of adult diabetes as have the sulfonylureas. There are a few reports of the successful use of DBI in the presence of acromegaly, labile juvenile diabetes, and diabetes of high insulin requirement (Krall, White and Bradley[4], Odell *et al.*[6], Pomeranze, Fujiy and Mouratoff[7] and Skillman *et al.*[8]). For these reasons it was felt that DBI might be of use in the treatment of varieties of diabetes other than the stable adult form, and to evaluate this idea we have selected patients for treatment on the basis of the severity, lability, or etiology of their disease. The response of the first 32 of this selected group is the basis of this report.

Methods. Patients were selected for treatment with DBI* from one of the following four groups:

Group 1 consisted of 12 patients with established labile diabetes subject to frequent insulin reactions and frequent episodes of acidosis with subsequent poor control.

Group 2 contained 8 patients whose diabetes had its onset following pancreatectomy (4 patients) or acute intermittent pancreatitis (4 patients) none of whom had a family history of diabetes.

Group 3 contained 10 patients whose daily insulin dosage was well established at 50 or more units, most of whom had experienced difficulty in achieving adequate control. The average daily insulin dosage was 63.8 units, with a range of from 50 to 105 units per day.

Two patients with stable diabetes were selected because of their failure to respond to tolbutamide. In addition, 2 patients in group 3 had shown a similar lack of response to tolbutamide. Those selected had been hospitalized for a variety of reasons, the majority for treatment of conditions directly related to diabetes mellitus. All patients remained

*DBI for this study was furnished by the U.S. Vitamin and Pharmaceutical Corporation, New York, New York.

hospitalized during the initial period of DBI administration usually for 8 to 10 weeks until its success or failure could be established, except for one patient who had his entire course of DBI as an outpatient.

Each patient had a thorough history and physical examination and all patients were maintained on a constant diabetic diet before and during treatment. At least 3 control determinations of fasting blood sugar and 24-hour urine sugar as well as control values for creatinine, alkaline phosphatase, Bromsulphalein retention, direct and indirect bilirubin, cephalin flocculation, thymol turbidity, complete blood count and urinalysis were obtained prior to initiation of DBI therapy.

TABLE 1.—PREVIOUS INSULIN DOSAGE IN 32 PATIENTS

Insulin Dosage	*No. of Pts.*
0 to 24 units	5
25 to 49 units	9
50 to 75 units	13
Over 75 units	5

Following the initiation of therapy, while the patients remained hospitalized, daily fasting blood sugars and 24-hour urine sugars were obtained for 3 to 5 days and 3 times weekly thereafter. In addition, weekly determinations of serum creatinine, alkaline phosphatase, bilirubin, cephalin flocculation, thymol turbidity, Bromsulphalein retention, complete blood count and urinalysis were obtained on all patients while hospitalized. Following discharge, those patients being maintained on DBI were seen at 2- to 4-week intervals at which times fasting blood sugars and 24-hour urine sugars were obtained.

Treatment in most cases was initiated with 25 to 50 mg. DBI given three times daily with meals. Insulin dosage was decreased an average of 10 units on the first day and, if indicated, by 10 to 15 unit increments thereafter if control of diabetes appeared adequate as DBI dosage was increased. If tolerated initially, DBI dosage was increased at 2- to 4-day intervals, usually by 25 to 75 mg. per day until control was achieved without added insulin, or until side effects became intolerable. When side effects appeared early, but seemed to be transient, or when there appeared to be a definite improvement in the control of the patient's diabetes with the combined use of insulin and DBI, the dosage of DBI was lowered from symptomatic levels to alleviate apparent side effects. If, after side effects appeared, there seemed to be no advantage to the patient in the continued use of DBI it was discontinued.

Results. The 32 patients ranged in age from 20 to 64 years, with an average age of 41. All but 4 patients were male and there were 8 Negro patients. Duration of diabetes was from 1 month to 24 years, averaging 6.9 years. Age at onset of diabetes ranged from 9 to 58 years, with an average of 35.1 years. There were 7 patients with age at onset of diabetes below 20 years. Previous insulin dosage may be seen in Table 1. The range was from 20 to 105 units per day, the average 52.3.

TABLE 2.—THE RESPONSE OF 32 SELECTED DIABETICS TO DBI. CLASS I: SUCCESSFUL RESPONSE. CLASS II: HYPOGLYCEMIC EFFECT, BUT SIDE EFFECTS INTOLERABLE. CLASS III: DBI FAILURE DUE TO SIDE EFFECTS OR ACIDOSIS

		Response to DBI		
Group	*No. of Patients*	*Class I*	*Class II*	*Class III*
1—Labile diabetics	12	3	7	2
2—Pancreatic	8	4	3	1
3—High insulin	10	4	4	2
Tolbutamide failure	4*	1	3*	
Total patients	32	12(38%)	15(46%)	5(16%)

*2 of these patients are included in other groups.

Patients were classified as to response to DBI in the following manner (Table 2):

CLASS I. These patients could be maintained at or below previous blood

sugar and 24-hour urine sugar levels on DBI alone, without insulin, and with transient or nonexistent side effects. Three patients with labile diabetes who could not tolerate a dosage of DBI great enough to eliminate insulin altogether were judged successful trials on smaller doses of DBI plus less than 50% of their previous insulin requirement. These patients achieved a significant improvement in their control as judged by elimination of frequent insulin reactions and periods of acidosis. Twelve of the 32 patients, or 38% gave this response.

CLASS II. In this group DBI was found to produce a significant hypoglycemic effect in that insulin dosage could be reduced 50% or more, but further increase in DBI was prohibited by the appearance of side effects. Since there was no apparent advantage to these patients in taking both DBI and insulin, they were classified as unsuccessful trials from the standpoint of clinical usefulness of the drug. Fifteen patients, or 46% were included in this response group.

CLASS III. This group includes those DBI failures in whom the development of acidosis on large doses (at least 300 mg. daily) or of severe side effects on smaller doses prevented administration of sufficient DBI to produce an antidiabetic effect as measured by significant reduction in insulin requirement. Five patients, or 16%, fell into this group.

The dosage range of DBI was from 75 to 300 mg. daily. No patient in this series could tolerate, if required, more than 300 mg. daily. The range of DBI dosage responsible for class I or II effects (production of hypoglycemic effect) was 75 to 300 mg. per day, with an average of 225. The patients in class I who have been successfully treated have remained continuously on DBI for 8 to 12 months at this time.

No significant correlation could be made between response to DBI and duration of diabetes, age at onset, or race. The results suggested, however, that patients whose previous insulin dosage was below 50 units per day had a higher percentage of successful responses (7 out of 14) than those whose insulin dosage had been more than 50 units daily (5 out of 18).

The presence of any symptom or sign unknown previously in the patient or possibly attributable to the administration of DBI was recorded by daily observations by the ward physician and the authors. All complaints by the patient which could not be attributed to previously known or coexistent conditions, or apparent aggravation of these were listed as possible side effects.

The side effects noted may be genrally classified as mild or severe.

Mild symptoms of anorexia, nausea, weakness, or drowsiness of transient nature lasting 1 to 4 days, usually occurring within the first 4 days of treatment, and disappearing spontaneously, were described by several patients.

Severe symptoms of anorexia, nausea, lassitude, weakness, drowsiness, vomiting and heartburn necessitated discontinuation of DBI in 17 of the 20 patients with class II or III response. In addition one patient developed a generalized urticarial eruption after 14 days of DBI treatment which disappeared rapidly upon withdrawal of the drug. One patient with substantiated arteriosclerotic heart disease complained of increased angina pectoris after 12 days of DBI, and one complained of the onset of symptoms of angina pectoris (not confirmed by electrocardiographic changes) after 4 months of successful DBI treatment.

Four patients while on DBI and insulin complained of a single episode of hypoglycemia, verified by true blood sugar levels of 34, 38, 40, and 47 mg.

per 100 ml. No hypoglycemic reactions were observed or reported in patients maintained on DBI alone. It is significant that only 3 of 32 patients had no complaints at any time which could be attributed to the use of DBI. These results are summarized in Tables 3 and 4. All side effects were rapidly reversed upon discontinuation or decrease in dosage of DBI. There were no instances of bone marrow depression or significant impairment of those renal or hepatic functions measured.

TABLE 3.—SEVERITY OF SIDE EFFECTS IN 32 PATIENTS

Side Effects	*No. of Pts.*
None	3
Mild	10
Moderate	12
Severe	7

control of blood sugar for this unfortunate group. It should be made clear that our early objective in therapy was to obtain control without insulin, and that results indicate that several of our labile diabetics classified as Class II responses would most likely have been able to achieve more stable control if smaller doses of DBI and continued insulin had been utilized.

2. A smaller percentage of patients requiring very large insulin dosage may respond satisfactorily to DBI alone, although we have been unable to predict these responses on the basis of our present observations.

3. The inherent high incidence of side effects with DBI leads us to believe that the mild adult onset diabetes should preferably be controlled with insulin or the sulfonylurea group

TABLE 4.—A NUMERICAL BREAKDOWN OF SPECIFIC SIDE EFFECTS FOLLOWING DBI ADMINISTRATION TO 32 PATIENTS

	Patients			*Patients*	
Symptoms	*No.*	*%*	*Symptoms*	*No.*	*%*
Anorexia	28	85	Hypoglycemia	4	13
Nausea	21	66	Heartburn	2	6
Lassitude	10	31	Angina Pectoris	2	6
Drowsiness	10	31	Diarrhea	2	6
Weakness	6	19	Myalgia	2	6
Headache	5	16	Urticaria	1	3
Vomiting	5	16			

Discussion. The number of patients studied in each group does not allow the derivation of conclusive formulae for the use of DBI. However, several clinical observations with relation to this group of patients seem of significance. Our experience suggests that the usefulness of DBI in therapy of diabetes mellitus may lie in the following applications.

1. A significant percentage of labile diabetics should be expected to tolerate an effective dose of DBI with concurrent insulin administration, which may provide closer and more stable

of oral antidiabetic drugs with a negligible incidence of side effects (Heineman *et al.*[2], Colwell *et al.*[1]). There may be a group of these patients unresponsive to the sulfonylureas in whom low doses of DBI may be effective.

4. DBI may be of use in the management of diabetics unable to take insulin because of blindness, neurological or other physical disability, or because of fat atrophy, and who prove unresponsive to other oral antidiabetic drugs.

It is of considerable interest to note that DBI is effective in a number of patients the onset of whose diabetes

followed pancreatectomy or pancreatitis. However, we cannot state with assurance that these patients are totally devoid of endogenous insulin.

The fact that a hypoglycemic effect (Class I or II response) was recorded in 27 of these 32 selected patients suggests that the biguanides may have wide applicability in the treatment of diabetes if the incidence of side effects can be reduced. The very high incidence of side effects in this series is probably due to the high dosage schedules used and the attempt to determine primarily the extent to which DBI could completely replace insulin in these types of patients.

The occurrence of an increase in the severity of angina pectoris in a patient with known arteriosclerotic heart disease in company with the report by Lambert[5] of electrocardiographic changes in 2 patients on chronic DBI therapy suggests the cautious use of DBI in the presence of this condition until more clinical and laboratory experience is gained.

The preceding suggestions for the clinical application of DBI are proposed only as a guide for further investigative use of this drug. No evidence is yet available of the long-term effects of DBI with regard to late side effects, incidence of diabetic complications, or longevity of patients treated chronically with the drug. Until these questions are answered in a significantly large group of patients, treated for a sufficient period of time with this interesting agent, our conclusions, and those of others, must remain tentative.

Summary. A preliminary report is presented dealing with the results of oral treatment of selected diabetic patients with phenethyldiguanide (DBI). Twelve patients with labile diabetes were treated, 3 having a successful response to DBI and lowered insulin dosage. Four of 8 patients with diabetes secondary to pancreatitis or pancreatectomy were controlled on DBI alone. Four of 10 patients on high insulin dosage (50 to 100 units per day) were controlled on DBI alone. One of 4 tolbutamide failures was successfully controlled on DBI. A high incidence of intolerable side effects was noted.

It is felt that DBI will be less useful in the therapy of stable adult diabetes because of the frequency of side effects, but that its best application may lie in the stabilization of labile diabetes, the regulation of some patients with high insulin requirement and in the management of diabetics physically unable to give themselves injections.

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SUMMARIO IN INTERLINGUA

Essayos Clinic con Phenethyldiguanido in Patientes Selegite

Es presentate un reporto preliminari super le uso oral de phenethyldiguanido (DBI) in le tractamento de selegite patientes diabetic. Dece-duo patientes con diabete labile esseva includite, e 3 de illes habeva bon responsas a DBI, resultante in reductiones de dosage de insulina. In 4 ex 8 patientes con diabete

secundari a pancreatitis o pancreatectomia, stabilisation esseva effectuate per DBI sol. In 4 ex 10 patientes recipiente alte dosages de insulina (inter 50 e 100 unitates per die), stabilisation esseva effectuate per DBI sol. Un de 4 patientes in qui tolbutamido habeva essite tentate sin successo, attingeva stabilisation per medio de DBI. Un alte incidentia de intolerabile effectos lateral esseva notate.

Es exprimite le opinion que DBI va esser minus utile in le therapia de patientes adulte con diabete stabile a causa del frequentia de effectos lateral. Su melior application es probabilemente in le stabilisation de diabete labile, in le regulation de certe patientes con alte requirimentos de insulina, e in le tractamento de diabeticos qui es physicamente incapace de inspicer se illes mesme.

SUMMARIO IN INTERLINGUA

(See page 153 for original article)

Respiration a Intermittente Pression Positive
Un Evalutation de su Uso in Therapia a Aerosol pro Chronic Emphysema Pulmonar

Le uso de apparaturas de respiration a intermittente pression positive de inspiration (RIPP/I = IPPB/I in le texto anglese) como adjuta pro administrar aerosol in le tractamento de chronic morbo pulmonar ha attrahite multe protagonistas depost su introduction in 1948. Depost ille tempore, le valor del effectos physiologic de RIPP/I ha essite establite plus specificamente in le tractamento de acidosis respiratori, in effortios de render le nebulation plus efficace in certe patientes, e in le preoccupation con problemas medical e chirurgic de hypoventilation. Le valor de therapia a aerosol ha essite definitemente confirmate, sed le valor supplementari del uso de RIPP/I in le nebulation routinari ha essite questionate e, de factor, effectos nocive de illo ha essite reportate in iste situation.

Esseva studiate le effectos producite in le function ventilatori per bronchodilatatores nebulate sub pression, administrate con e sin RIPP/I, in 29 patientes con emphysema pulmonar. Nulle significative differentias in le grado del melioration esseva demonstrabile inter le duo methodos. Le option del patientes quanto al plus efficace methodo non poteva esser correlationate con mesurationes objective.

In un secunde studio, alterationes del function ventilatori post nebulation a pression de un agente fictitie esseva comparate con e sin RIPP/I in 25 patientes con emphysema pulmonar. Esseva constatate nulle significative effectos benefic o nocive in le function ventilatori, attribuible al uso de RIPP/I. Alterationes del function ventilatori causate per factores psychologic e altere esseva demonstrate frequentemente in ambe le studios.

Le indicationes contra le uso de RIPP/I es pauco numerose. Illos include pneumothorace de data recente, hemorrhagia pulmonar, choc, e—in certe casos—reducite reserva cardiovascular. Studios preliminar in nostre laboratorio ha revelate in certe patientes un reduction del saturation oxygenic post RIPP/I a aere.

Ab le puncto de vista practic, le characteristicas de automatiso e de intermittentia del nebulation in RIPP/I, resultante in un economia de O_2 e de aerosol, rende iste apparato extrememente utile. Per le uso de basse pressiones in le masca (excepte in casos in que indicationes specific stipula altere requirimentos) e per le uso de O_2, iste apparato se ha provate salve, efficace, e convenibile in le therapia routinari a aerosol. Tamen, le necessitate es sublineate de individualisar le tractamento ab un caso al altere.

VARIABILITY OF DIURETIC RESPONSE AS INFLUENCED BY THE STATE OF THE ORGANISM

A NOTE ON THE LAW OF INITIAL VALUES

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In a comparative study of the effects of diuretic agents upon persons free of cardiac and renal disease, the degree of increase in urine volume induced by various potent compounds was found to vary widely from subject to subject despite precise control of fluid, caloric, and electrolyte intake. Attempts to correlate these deviations with the differences in the weights of the subjects, fluctuations in emotional state, or daily room temperature and humidity were unsuccessful. Instead, an inverse correlation was found between the volume of urine excreted under control or "basal" conditions, and that excreted in response to diuretic stimulation.

Method of Study. One hundred essentially healthy subjects were hospitalized for study on a metabolic ward where scrupulous care was accorded food and fluid ingestion and the collection of urine specimens.

During a 5-day-study period, each subject consumed a diet which provided 2,000 calories daily and contained 3.2 gm. of sodium, 4.0 gm. of potassium, and 4.0 gm. of chloride. The total daily liquid was 3,000 ml. On each day, careful observations of liquid intake, urine output, room temperature and humidity were made.

On the first day, the serum sodium, potassium, chloride, and nonprotein nitrogen were determined to be within normal limits, and the subject was weighed under standard conditions, that is, wearing only pajama trousers, after voiding, and prior to breakfast at 8:00 a.m.

Each morning thereafter, the weighing was repeated and the 24-hour (8:00 a.m. to 8:00 a.m.) urine collections were gathered for measurement of volume, specific gravity, and electrolyte content.*

*Data concerning the changes in electrolyte excretion in these studies are not included here. This information is the subject of another paper now in preparation.

The first 2 days of the study period were control days during which the subjects observed the requirements of the protocol, but on which they received neither diuretic nor placebo. The agent to be tested was administered by a double-blind technique on the third and fourth days. On the fifth day, no agent was given, but the subjects continued to observe the standard regimen.

Results. The data for one diuretic meralluride (Mercuhydrin), 2 ml. given intramuscularly are shown in

CONTROL PERIOD. Each subject was then classified as a "high," "medium," or "low" excretor depending upon the volume of urine voided under base line conditions on this second control day. Those whose urine volumes amounted to 75 to 95% of their fluid intake were arbitrarily designated as the medium group. An output greater than 95% placed the subject in the high group; less than 75%, in the low. The mean of

TABLE 1.—TWENTY-FOUR HOUR URINE VOLUME (EXPRESSED AS PERCENT OF 24-HOUR LIQUID INTAKE) FOR EACH OF 19 SUBJECTS WHO RECEIVED MERALLURIDE ON DAY 3 AND DAY 4. NOTE IN THE LAST COLUMN THE LARGE VARIATION IN THE RESPONSES OF THE INDIVIDUAL SUBJECTS TO THE FIRST DAY OF DIURETIC ADMINISTRATION (DAY 3)

	Day					
Subject	*1*	*2*	*3*	*4*	*5*	*% Change Day 2 to Day 3*
1	82	90	91	70	75	+ 1
2	23	53	83	54	25	+57
3	39	47	93	48	28	+98
4	111	116	106	86	64	− 9
5	98	72	98	82	74	+36
6	121	118	107	111	83	− 9
7	69	79	102	63	48	+29
8	105	99	113	75	80	+14
9	95	78	98	100	88	+26
10	111	102	103	80	55	+ 1
11	90	90	96	84	93	+ 7
12	91	88	93	56	53	+ 6
13	53	85	117	83	68	+38
14	102	71	109	78	63	+54
15	123	112	126	83	83	+13
16	93	91	91	87	72	0
17	121	109	109	94	108	0
18	134	87	105	68	56	+21
19	82	65	102	58	65	+57

Table 1. The diuretic response expressed as percent of change in urine output from Day 2 (control) to Day 3 (treatment) varies all the way from a minus 9% to a plus 98%.

By statistical analysis of these data, it was shown that a significant negative or inverse correlation exists between the control urine volume on Day 2 and the magnitude of diuretic response on Day 3 (Fig. 1).

the urine volumes excreted by all subjects in each group was calculated for each of the 5 days of the study, and the results tabulated (Table 2). Linear graphs (Fig. 2*a*, *b*, *c*, *d*) were then constructed from this table.

PLACEBO DATA. Figure 2*a* is such a graph representing the results obtained when a placebo was administered on the third and fourth days. Note that although there was some fluctuation

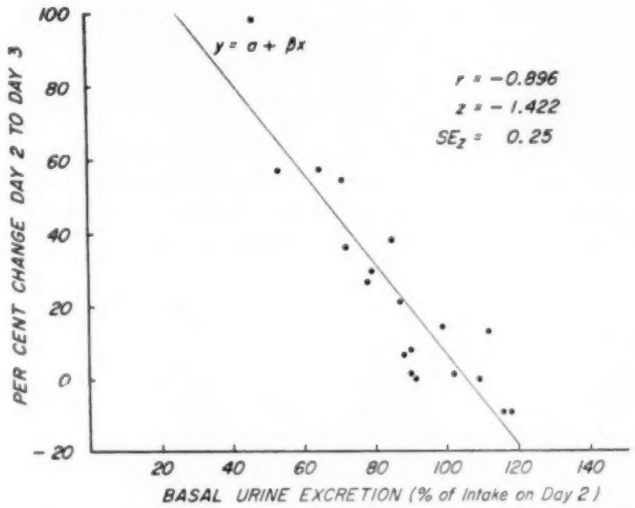

Fig. 1.—A scatter diagram illustrating the negative correlation between the control urine volume and the magnitude of response to meralluride.

TABLE 2.—THE MEAN URINE VOLUME (EXPRESSED AS $\frac{\text{OUTPUT}}{\text{INTAKE}} \times 100$) FOR EACH GROUP, WITH THE SUBJECTS IN EACH GROUP SUBDIVIDED INTO HIGH, MEDIUM, OR LOW EXCRETORS ACCORDING TO THE VOLUME OF URINE VOIDED UNDER THE BASAL CONDITIONS OF THE SECOND CONTROL DAY

	No. of Subjects	*Group*	*Day* 1	2	3	4	5
Placebo	5	High	98	105	94	95	92
	24	Medium	84	86	81	81	82
	13	Low	64	60	73	68	69
Meralluride	6	High	115	109	111	88	79
	8	Medium	88	86	99	77	69
	5	Low	69	67	97	64	51
Acetazolamide	4	High	100	101	103	80	79
	9	Medium	78	83	106	83	75
	8	Low	63	66	95	77	72
Mercaptomerin	5	High	104	103	114	92	80
	9	Medium	81	86	99	75	69
	4	Low	68	71	91	64	57

until stabilization was reached, the high, medium, and low excretor groups retained their separate identities in a remarkably consistent manner throughout the study period. The high group tended to excrete less urine on the first placebo day than on the control day; the low group tended to excrete more than the control amount.

lowing the increase of the third day, all groups entered a sharp decline, perhaps representing a recuperative replacement of water into the depleted body stores.

B. Acetazolamide. The administration of acetazolamide (Diamox), 250 mg. t.i.d. on the third and fourth days, produced the responses noted in Fig.

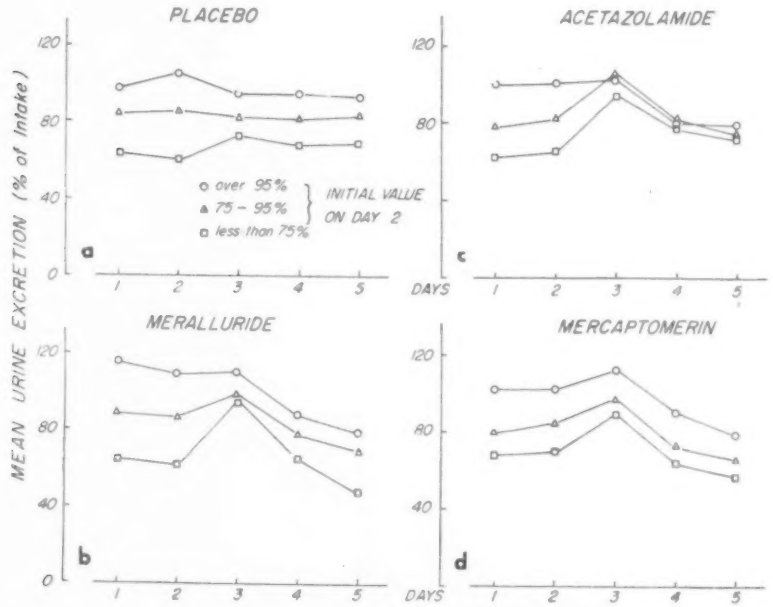

Fig. 2.—Urine excretion patterns of "high," "medium," and "low" excretor groups in placebo and diuretic studies.

DIURETIC DATA. *A. Meralluride.* Figure 2*b* illustrates the results when meralluride, 1 ml., was administered intramuscularly at 8:00 a.m. and 4:00 p.m. on the third day and at 8:00 a.m. on the fourth. Here the inverse relationship between the basal volume and the magnitude of the diuretic response is clearly demonstrated. The group with the low initial value had a mean volume increase of 34.60%. During the same interval, the medium group responded with a mean increase of 13.13%, and the high group with only 1.33%. Fol-

2*c*. Results similar to those seen with meralluride are noted; the low group had a mean gain of 29.12%, and the high group, 2.0%. The same withholding effect was noted after diuresis.

C. Mercaptomerin. Mercaptomerin (Thiomerin), 1 ml., given intramuscularly at 8:00 a.m. and 4:00 p.m. on the third day and at 8:00 a.m. on the fourth, also produced a similar pattern of responses. The low group had a mean increase of 19.75%, the medium group, 13.44%, and the high group, 10.80% (Fig. 2*d*).

After noting this pattern of response in our current study, the data obtained by Clark and Hagans[1] in earlier diuretic studies were re-examined and found to conform to the same pattern when the two similar drug studies (Mictine 1.2 gm., Rolicton 1.2 gm.) were combined to produce an adequate number (22) of observations (Fig. 3).

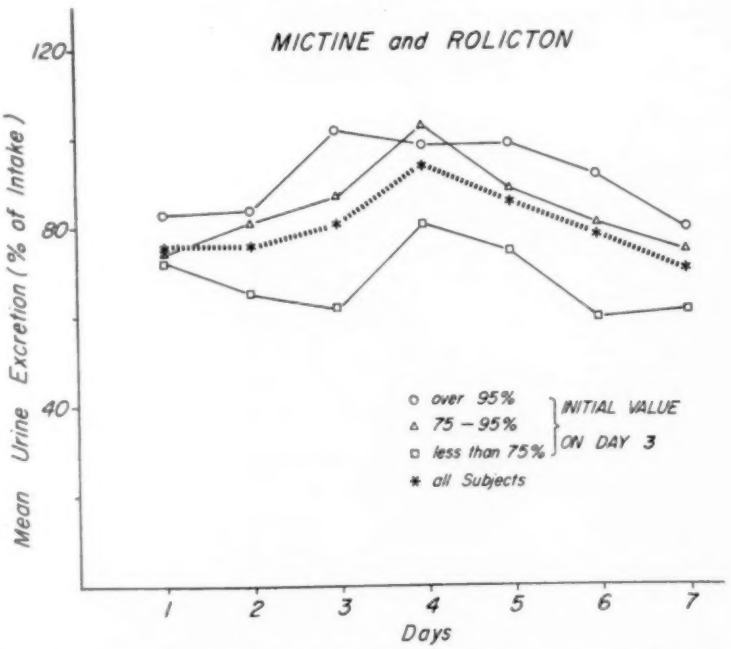

Fig. 3.—Diuretic response to Mictine and Rolicton. The agents were administered on the 4th, 5th, and 6th days after 3 control days. Data from the studies of each drug were combined to prepare this graph.

THE LAW OF INITIAL VALUES. The biologic phenomenon observed here was designated "The Law of Initial Values" by Wilder in 1931[5]. In the years following his initial description Wilder and other investigators have repeatedly observed manifestations of this rule in a variety of stimulus-response situations[6]. In the case of the diuretic data presented here, it would appear that powerful homeostatic forces may be tending to maintain fluid balance, opposing the diuretic when the urine volume of the control day was very high, and conversely reinforcing the diuretic when the control volume has been low and the body stores of water presumably adequate. Certainly the observation is of great practical value in the study of pharmacodynamic agents. If the state of biologic balance during the control period is not taken into account, effects may wrongly be attributed to an agent or effects of an agent may be obscured or overlooked.

Most frequently, the responses obtained in drug evaluations are expressed in terms of mean values, but unless the means are derived from similarly proportioned groups of observations with respect to initial values, it is evident that they will not be comparable. Further, a disproportionate

number of subjects in either the high or low range of the "initial values" will distort the interpretation of the true potency of a drug, engendering false conclusions in the individual experiment. If, for example, the four "high excretor" subjects in the meralluride experiment are eliminated, the mean increase in urine volume rises from 16% to 24%, and conversely, if the higher are allowed to remain and the

A promising approach was offered in a monograph by Lacey in 1956[2]. The use of the analysis of co-variance has also been recommendd by Snedecor[4] and by Rao[3].

The following technique has been found satisfactory in this situation, and may have general applicability.

CORRECTION FOR THE LAW OF INITIAL VALUES. Examination of the data obtained in the 42 placebo tests disclosed

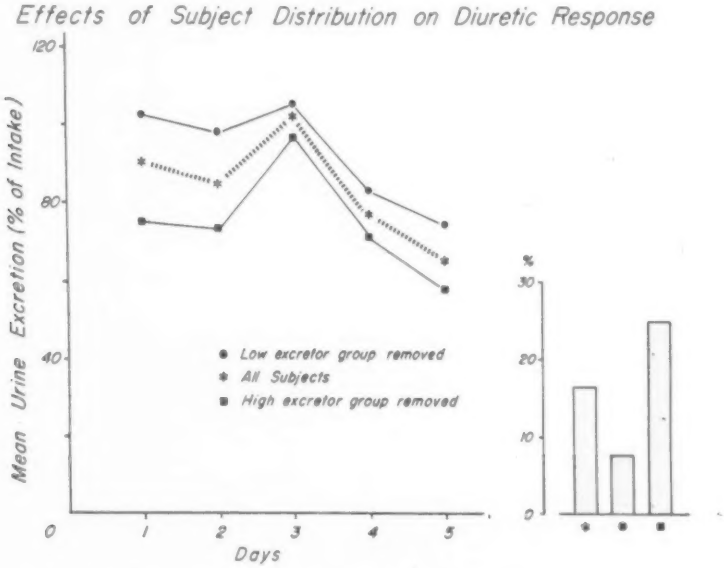

Fig. 4.—Removing the "low excretor" group lowers the mean response by 50%. Removal of the "high excretor" group increases the mean response by 50%.

"low excretors" are removed, the mean increase declines to 8% (Fig. 4). Parallel alterations of mean diuretic effect occur if the acetazolamide or mercaptomerin data are similarly treated.

As it often is not feasible to obtain ideal distributions of subjects in various treatment groups, some statistical method which will compensate for the effect of initial values is desirable. In his original paper, Wilder presented no procedure of this sort for managing the influence of the initial values effect.

a significant positive correlation between the volume of urine excreted on Day 2 and Day 3 (Fig. 5). Those subjects having small control volumes on Day 2 tended to have small volumes on Day 3; those with large Day 2 volumes tended to have large volumes on Day 3 when the placebo was administered.

In Fig. 6 these same Day 2 urine volumes have been arranged in order of ascending magnitude and their corresponding Day 3 volumes plotted.

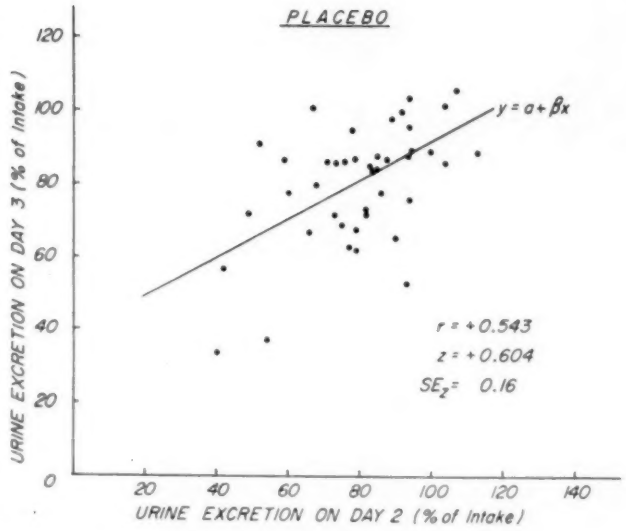

Fig. 5.—Correlation of urine volumes between Day 2 and Day 3 in the placebo study.

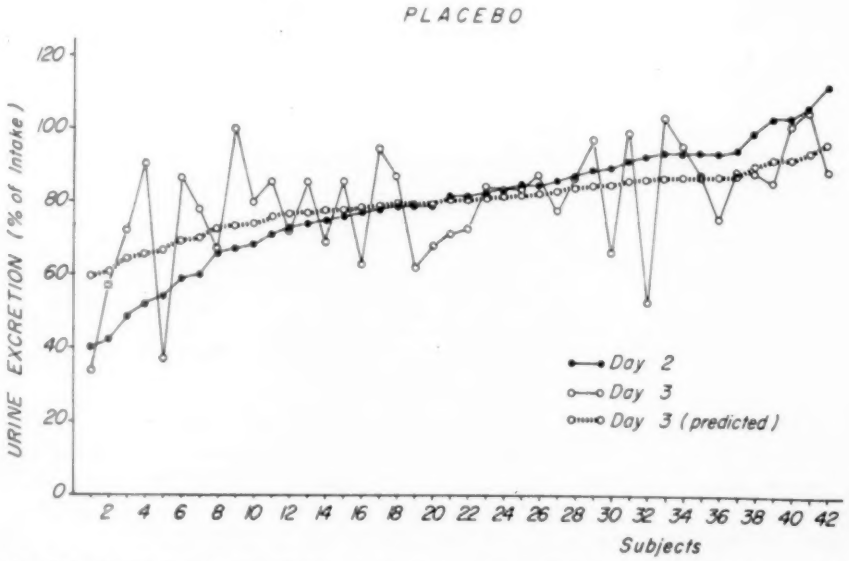

Fig. 6.—The observed and predicted Day 3 urine volumes plotted against their corresponding Day 2 volumes in the placebo study. These predicted values plotted along the dotted line represent a continuous mean of the peaks and valleys of the observed Day 3 urine volumes.

From the regression equation, $y = a + bx$ a *predicted* Day 3 volume was calculated from each of the Day 2 volumes, and these are shown along the dotted line. This represents in effect a continuous calculated mean based upon the actually observed Day 3 volumes. This regression equation was then applied to the data obtained from the groups receiving the diuretic agents, and from each Day 2 control volume, a Day 3 volume was calculated which would then represent the volume of urine expected had that subject *not* received a diuretic drug.

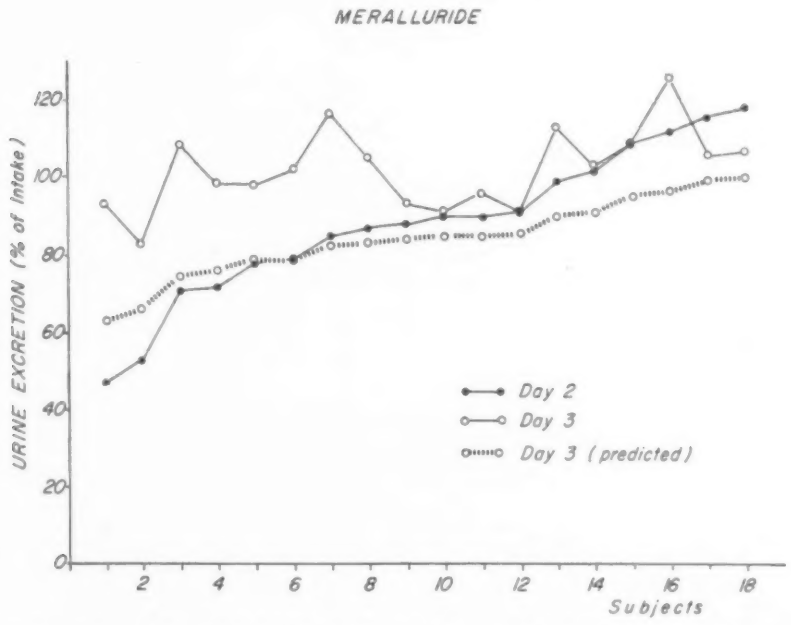

Fig. 7.—Correction of the "Initial Value" effect in the meralluride study. Data derived from regression analysis of the placebo study were applied to the meralluride group to provide the predicted Day 3 responses shown along the dotted line. Here $a = 38.95$ and $b = 0.517$. y is the predicted Day 3 value and x is the initial (Day 2) value. Note that using the differences between the observed and predicted Day 3 volumes provides a much more regular pattern than does using the observed Day 3 minus Day 2 differences.

An example using the meralluride data is illustrated in Fig. 7. In the case of the first 5 subjects, there is a measurable difference between the Day 2 volume and that increase which would be expected on Day 3 even if no diuretic had been given. This portion of the increase should probably not then be included as diuretic effect, and instead, only the difference between the actually observed Day 3 volume and the predicted Day 3 volume should be counted. On the other hand, the predicted Day 3 response for subjects 7 through 18 is less than their Day 2 volumes, and subtraction of the predicted from the observed Day 3 volumes yield greater differences than does subtracting the Day 2 from the observed Day 3 volumes. Utilization of this procedure then, produced a greater similarity in the responses throughout the entire spectrum of con-

trol volumes. The t-test for paired controls may then be applied, using the volumes observed on Day 3 minus the expected Day 3, rather than observed Day 3 minus observed Day 2. This takes into account a correction with respect to the initial value of each subject and permits a more valid interpretation of the response observed. When one performs such a test on the placebo data, of course, the t value is small and indicates no significant difference between the observed and the expected Day 3 values. In the case of meralluride, a t value of 4.992 was obtained, indicating a significant increase in urine volume on Day 3 ($p<.001$). This was a larger t value than that obtained using observed Day 3 values minus observed Day 2 values (here: $t = 3.651$). In some instances the t-test for paired controls using the differences between observed Day 2 and Day 3 urine volumes led to an insignificant t value. Retesting these data using the differences between the observed Day 3 and predicted Day 3 urine volumes led to a significant t value, thus revealing the pharmacodynamic effect of the diuretic which had been masked by the usual statistical analysis.

Conclusions. The response to diuretic stimulation of the healthy human kidney is influenced by the basal level of activity in that organ. An inverse correlation has been found to exist between the volume of urine excreted under basal conditions and the amplitude of water diuresis following the administration of a diuretic agent.

The use of data obtained in placebo tests provides a technique whereby it is possible to calculate the volume of urine to be expected following a control period, if no diuretic was administered, and thereby to differentiate a response to an effective stimulus. Correcting for the initial values effect in this manner permits the recognition of pharmacodynamic activity which might otherwise be masked.

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SUMMARIO IN INTERLINGUA

Le Stato del Organismo Como Factor de Influentia Super le Variabilitate del Responsa Diuretic

Un Nota Super le Lege del Valores Initial

Le responsa a un stimulation diuretic de normal renes human es influentiate per le nivello basal del activitate in ille organo. Esseva trovate que un correlation inverse existe inter (1) le volumine de urina excernite sub conditiones basal e (2) le amplitude del diurese de aqua post le administration de un agente diuretic.

Le uso de datos obtenite per medio de tests con placebos provide un technica que rende possibile calcular le volumine de urina a expectar post un periodo de controlo si nulle diuretico es administrate e assi differentiar le responsa evocate per un stimulo efficace. Iste maniera de introducer correctiones pro le effecto del valores initial permitte le recognition de activitate pharmacodynamic que alteremente remanerea forsan mascate.

ANTIBIOTIC SENSITIVITIES OF STAPHYLOCOCCI ISOLATED BEFORE AND AFTER PATIENTS WERE GIVEN ANTIBIOTICS

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THE question asked in this study was: Does the administration of an antibiotic to a patient cause a change in the antibiotic sensitivity of staphylococci that are infecting that patient? Data were obtained by comparing the antibiotic sensitivities of staphylococci* that were isolated from patients before and after they were given the antibiotics to determine what changes in sensitivity had occurred. Many reports cite instances in which increased drug resistance occurred after antimicrobial therapy, but we found few reports that detailed the number of instances in which repeat cultures have shown the same or decreased resistance after the administration of an antibiotic (Anderson, Howard and Rammelkamp[2], Findlay and Johnson[9], Haight and Finland[10]). No attempt will be made to review the general literature on changes in the antibiotic sensitivity of bacteria, as it has been done elsewhere (Chain, Florey and Jennings[5], Finland[7]). Instead, articles will be referred to in the presentation of our results that are pertinent to these results.

The necessity for the foregoing study might be questioned by those who already have made recommendations regarding antibiotic usage that are based on the assumed influences of antibiotic usage on antibiotic resistance of bacteria, but it is our feeling that these influences should be further scrutinized before their existence can be fully accepted.

Materials and Methods. Fifty patients in whom coagulase-positive staphylococci were isolated before and after treatment with antibiotics were studied. Their diagnoses were about equally divided between chronic bacteremias, chronic osteomyelitis, and wound infections, and no differences in results were found in any one of these groups. The sensitivities to antibiotics of the "before and after" strains were determined by the tube dilution method for determining bacterial sensitivity to antibiotics (Waisbren, Carr and Dunnette[18]). The differences between the two cultures in regard to the sensitivity to antibiotics were noted and an attempt was made to correlate these differences with antibiotics that were given to the patient. All changes were noted since the data were analyzed collectively. Thus the variation due to the method was taken into account without the loss of the chance to pick up subtle differences that might have shown up if in each case the second culture would have been just one tube more resistant.

An attempt also was made to determine if fewer changes in antibiotic resistances occurred when more than one antibiotic was given at the same time.

*All staphylococci referred to in this paper were *Staphylococcus pyogenes* var. *aureus* and were coagulase positive.

Several difficulties are inherent in this method of study and they should be pointed out before the results are presented. The first is that there is no definite proof that a second culture of staphylococci isolated in the patient was in any way derived from the first culture. It may always have been re-infection. This difficulty was not met fully but in the 14 cases when just staphylococci isolated from the blood were compared, there was no essential difference in data. In these cases we felt it less likely that re-infection was a contributing factor. The second difficulty was that in some cases the antibiotic that was given may never have made contact with the staphylococci that subsequently were isolated. The experience with streptomycin which will be presented first, we feel, offers some evidence that in most cases some contact between the administered antibiotic and the staphylococci was made.

The total dosage of antibiotics used in each case was noted and these ranged from the usual therapeutic dose to what might have been considered massive dosages. However, no correlations were apparent between dosages and changes in resistance. Similarly, the lengths of time between the two cultures and between stopping the antibiotic and the second culture were noted. The time between the two cultures was, in the majority of the cases, less than one month and the second culture was usually within a month after the antibiotic had been given. No conclusive information was obtained regarding relationships between dosages and times between cultures, so these complicated and confusing figures will not be detailed in this presentation.

The data to be presented concern the differences between antibiotic sensitivities of staphylococci isolated before and after the administration of penicillin, chloramphenicol, erythromycin, streptomycin, neomycin, oxytetracycline, chlortetracycline, novobiocin, nitrofurantoin and carbomycin.

The number of times combinations of antibiotics were used to which the initial culture was sensitive was noted to see whether or not these combinations prevented increases in antibiotic resistance and these results also will be presented.

Results. 1. THE DIFFERENCES BETWEEN THE SENSITIVITIES TO ANTIBIOTICS OF 50 CULTURES BEFORE AND AFTER ANTIBIOTICS WERE USED. There were 152 instances when determinations were available before and after one of eight antibiotics was administered. Thus, an average of three antibiotics had been given to each patient. In 53 of the 152 instances there was no change in the sensitivity of the second culture to the antibiotic that had been given. In 42 of the 152 instances, the second culture was more sensitive, and in 57 cases the second culture was more resistant to an antibiotic that had been given (Fig. 1). These figures, and even a casual perusal of Fig. 1 discourage a statement regarding a general effect of the administration of antibiotics on antibiotic sensitivity of staphylococci.

As a control, the sensitivities of the staphylococci to antibiotics the patient did not receive were studied. Unrelated antibiotics were chosen in each case so that the data on only 127 usages were available. For instance, when the patient received penicillin, differences in resistance to chloramphenicol were noted. The unrelated antibiotics used as controls were as follows: tetracycline control for streptomycin, chlortetracycline control for erythromycin, and chloramphenicol control for erythromycin.

In 32 of 127 instances no change in sensitivity was noted. In 40 cases the second culture was more sensitive to the control antibiotic and in 55 cases the second culture was more resistant to the control antibiotic (Fig. 1). In Table 1 the figures for changes with all the antibiotics and their controls are reduced to percentages and it is interesting to note that almost as many strains became more resistant to antibiotics that the patients did not receive as to antibiotics that they did receive, and that the differences were not significant (Table 1) (P-Value$>$.05).

2. RESULTS WITH EACH ANTIBIOTIC. Data in regard to each antibiotic were separated into instances in which the initial culture was clinically susceptible to the antibiotic and those in

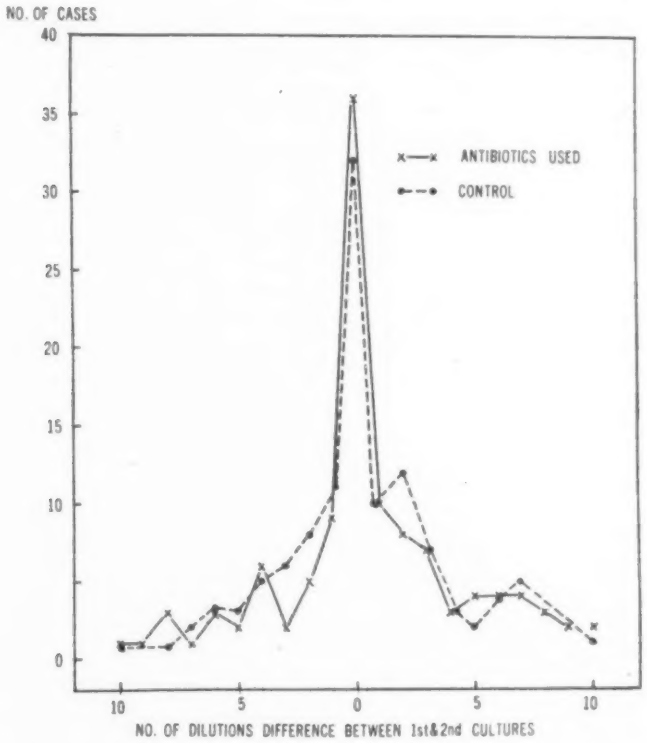

Fig. 1.—The numbers of strains of staphylococci that became more sensitive to, more resistant to, or stayed stationary in their sensitivity to antibiotics administered to patients who harbored them. The horizontal axis to the right of "O" represent the number of dilutions more resistant the second culture was, and the horizantal axis to the left of "O" represents the number of dilutions more sensitive the second culture was.

TABLE 1.—COMPARISON BETWEEN PERCENTAGES OF STRAINS THAT BECAME MORE RESISTANT TO ANTIBIOTICS THE PATIENTS RECEIVED WITH THOSE THAT BECAME RESISTANT TO ANTIBIOTICS THAT WERE NOT GIVEN.*

	% *No Change*	% *More Resistant*	% *More Sensitive*
Antibiotics Patients Did Receive	34	38	28
Control Antibiotics Patients Did Not Receive	25	33	32

*Analysis by the Chi square method showed no significant differences.

which the initial culture was resistant to the antibiotic (Table 2). Figures for clinical sensitivity that had been based on our previous experiences were arbitrarily used (Waisbren[17]). This was done because, from a clinical standpoint we were most interested in what happens when a patient is given an antibiotic to which his infecting staphylococci are clinically sensitive. Therefore, in the discussion of each antibiotic, the results with initially sensitive bacteria will be emphasied.

Streptomycin. The results with streptomycin are exactly what should be expected, since soon after streptomycin was discovered, rapid increases in resistance to it in patients who were treated were noted (Finland *et al.*[8]) (Table 2). As mentioned before, however, the fact that in all 5 cases in which the initial culture was sensitive the second culture was markedly more resistant tends to validate our data by showing that in this group of patients the drugs usually made contact with the staphylococci. The rapid mutation rate in regard to streptomycin resistance is apparently a relatively unique phenomenon that explains the mechanism by which rapid changes in resistances to streptomycin occur (Demerec[6]). However, antibiotics that are even as closely related to streptomycin as is neomycin do not have this rapid mutation rate in regard to antibiotic resistance, so generalizations based on this apparently very special case are not justified (Waisbren and Spink[19]).

Penicillin. In 8 out of 9 cases in which the initial culture of staphylococcus was sensitive to penicillin, the second culture was more resistant to penicillin after therapy with this antibiotic (Table 2). In these cases, there remains the question as to whether or not re-infection occurred in every case. Four of the 9 strains were from blood cultures and in these re-infection of course must be considered less likely.

Four of these paired cultures were phage-typed* and in no case was the phage-type the same in the before and after culture. Unfortunately, none of the paired cultures that were typed were both from the blood. In these cases, then, an original mixed culture or a re-infection might be considered the most likely explanation for the change in penicillin sensitivity.

Changes from penicillin sensitivity to penicillin resistance to staphylococci after treatment with penicillin had been reported many times in the literature (Anderson, Howard and Rammelkamp[2], Rammelkamp and Maxon[13], Spink, Hall and Ferris[14]). These publications, however, did not detail the number of instances in which repeat cultures still were sensitive to penicillin, so no strict comparisons of data can be made. The role of penicillinase in regard to penicillin resistance has been the subject of much discussion. It has been emphasized that, *in vitro*, no demonstration of how penicillin sensitive, non-penicillinase producing organisms might become penicillin resistant and penicillinase producing has as yet been demonstrated (Barber[3]). The studies of Szybalski[16] have shown that in a large number of non-penicillinase producing organisms, a few penicillinase producers are often present. This may explain how our findings came about since the penicillin producers might have emerged when the sensitive organisms were killed by the penicillin. Spink, Hall and Ferris[14] have shown that exposure to penicillin will increase penicillinase production and this, of course, may explain the phenomenon that was observed. We con-

* Through the courtesy of Dr. Marie Koch, Veterans Administration Hospital, Wood, Wisconsin.

TABLE 2.—SUMMARY OF DATA REGARDING THE SENSITIVITIES OF STAPHYL

Antibiotic	*Total number of times sensitivity determinations where available before & after the antibiotic was given*	*Changes in the group of cultures as a whole. Number of times a culture showed*		
		No change	*More sensitive*	*More resistant*
Streptomycin	20	6	7(5,1,1,5,1,3, 2)*	7(7,2,8,7,7,3, 1)
Oxytetracycline	9	2	3(1,6,6)	4(1,2,4,2)
Chlortetracycline	9	1	4(4,5,1,3)	4(2,3,1,4)
Chloramphenicol	32	14	9(1,1,6,6,1,8, 2,4,1)	9(3,2,3,1,2,4, 1,3,1)
Erythromycin	21	5	5(1,2,1,2,9)	11(8,10,8,4,5,6, 1,7,9,4,2)
Penicillin	39	11	15(7,6,3,1,8,8, 4,4,4,1,2,5, 5,4,10)	13(2,1,6,6,9, 10,3,6,5,5, 5,1,4)
Neomycin	14	4	1(4)	9(2,2,1,3,1,3, 2,3,1)
Novobiocin	8	5	1(2)	2(4,1)
Carbomycin	6	2	1(2)	3(1,1,1)
Nitrofurantoin	4	3	1(2)	0

*The numbers in the parentheses show the number of tube dilutions difference between the first and second culture in all columns.

[00]The number of cases in which the organism changed from clinically sensitive to clinically resistant by our arbitrary standards[19] are in the starred parentheses, *i.e.* ( )*

sider staphylococci sensitive clinically to penicillin that are inhibited by a concentration as high as 3 μg. per ml. This figure has been derived from study of staphylococcic bacteremias (Abboud and Waisbren[1]). Some cases that respond to penicillin, therefore, must be penicillinase producers and it might be that in some of the cases that we have reported the initial strains were weak penicillinase producers whose ability to produce this important enzyme was stimulated by the exposure to the drug (Bondi and Dietz[4]).

In summary then, the experience with penicillin shows that in 8 out of 9 cases in which repeat cultures were obtained in which the initial culture was sensitive to penicillin, a second culture taken after this drug was given revealed the organism to be more resistant. These data suggest the following possibilities: (1) The original infecting culture may have been a weak penicillinase producer that was stimulated to increase its production of this enzyme by exposure to penicillin (Spink, Hall and Ferris[14]), (2) There may have been a few penicillinase producers in the original cultures that were "selected out" by penicillin therapy (Szybalski[16]), (3) That re-infection occurred in every case, or (4) That the original non-penicillinase producers in some way change their characteristics to produce this enzyme. The last possibility is thought to be most unlikely, due to the inability of investi-

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Changes among the cultures that were initially sensitive to the antibiotic				*Changes among the cultures that were initially resistant to the antibiotic*			
No.	*No change*	*More sensitive*	*More resistant*	*No.*	*No change*	*More sensitive*	*More resistant*
5	0	0	(5)* 5(7,2,8,7,7)	15	6	(2)* 7(5,1,1,5,3,2)	2(3,1)
3	1	1(1)	(1)* 1(1)	6	1	(0) 2(6,6)	3(2,4,2)
3	0	1(4)	(1)* 2(3,3)	6	1(1)	(1)* 3(5,1,3)	2(1,4)
25	11	5(1,1,1,6,1)	(3)* 9(3,2,3,1,2,4, 1,3,1)	7	3	(0)* 4(8,2,4,1)	0
13	1	3(1,2,1)	(4)* 9(8,10,8,4,5, 6,1,7,9)	8	4	(2)* 2(2,9)	2(4,2)
9	1	0	(5)* 8(2,1,6,6,9, 10,3,6)	30	10	(9)* 15(7,6,3,1,8,8, 4,4,4,1,2,5, 5,4,10)	5(5,5,5,1,1)
14	4	1(4)	(1)* 9(2,2,1,3,1,3, 2,3,1)	0			
6	4	0	(2)* 2(4,1)	2	1	(1)* 1(2)	0
4	2	0	(0) 2(1,1)	2	0	(0) 1(2)	1(1)
4	3	1(2)	0	0			

*( )Starred numbers in the parentheses show number of strains that changed from clinically sensitive to clinically resistant or vice versa.

gators to demonstrate this phenomenon *in vitro* (Barber[3]).

Erythromycin. In 13 cases in which erythromycin was used, an initially sensitive strain was isolated, and in 9 of these cases the post therapy culture showed increased resistance. This would appear to confirm numerous articles that suggest increased resistance to erythromycin during therapy is not uncommon (Haight and Finland[10], Martin *et al.*[12]). Neither mutation nor the production of an inhibitor have been indicted as the *in vitro* cause of the erythromycin resistance. During the course of this study, staphylococci in our hospital became more resistant to erythromycin so re-infection with organisms of increasing resistance was not unlikely (Waisbren[17]). However, until more information regarding the specific modes of staphylococcic resistance to erythromycin is available, it is idle to speculate on the whys and wherefores of these data.

Chloramphenicol. Nine of 25 cases, in which the staphylococci were initially sensitive, showed increasing chloramphenicol resistance on the repeat culture. Although these numbers are too small for generalization, they are in line with previous experiences that show staphylococci to be relatively more stable in regard to chloramphenicol resistance than with erythromycin resistance (Waisbren[17]).

Neomycin. Nine out of 14 cultures initially sensitive to the neomycin were

more resistant after therapy with this drug. Only one of these 9 strains became resistant to greater than 3 μg. per ml. of neomycin, a level which in our studies denotes clinical resistance (Waisbren and Spink[19]). This is consistent with previous experience that showed staphylococci to be almost uniformly sensitive to this antibiotic (Waisbren[17]).

Experiences with strains initially sensitive to the other agents were too limited even to attempt generalizations but they are recorded in detail in Table 2 and are included in our composite figures (Fig. 1).

3. THE INFLUENCE OF COMBINED ANTIBIOTICS ON CHANGES IN RESISTANCE. This was studied by comparing the cases in which the initial culture was sensitive to an antibiotic and in which this single antibiotic was given, with the cases in which the initial culture was sensitive to two antibiotics that were given. Seventeen of the former instances were found and the repeat cultures were resistant in 5 of them, whereas 27 of the latter instances were found and in 14 of these cases there was increased resistance to one or the other, or both the administered antibiotics. Thus, the combination of antibiotics was not shown to prevent increases in antibiotic resistance (Table 3).

TABLE 3.—THE EFFECT OF COMBINING ANTIBIOTICS ON THE SUBSEQUENT DEVELOPMENT OF RESISTANT STRAINS

Number of cases in which the first culture was sensitive to a single administered antibiotic.	*Number of times the repeat culture was resistant to that antibiotic.*	*Number of cases in which the first culture was sensitive to two administered antibiotics.*	*Number of times the repeat culture was resistant to one or both of the administered antibiotics.*
17	5 (29%)	27	14 (52%) (8 times to one of the antibiotics 6 times to both of the antibiotics)

Discussion. Perhaps the most important point emphasized by these rather limited data is that there does not appear to be an *a priori* relationship between the administration of antibiotics to patients and the subsequent isolation of staphylococci resistant to antibiotics from these patients. This was somewhat surprising to us because we had turned to the individual patient as the possible ecologic niche in which resistant organisms could be selected out and established when we were unable to relate antibiotic usage within a hospital to changes in antibiotic sensitivities in that hospital (Waisbren[17]).

Our data may seem, at first glance, to be contrary to studies that showed a direct relationship between hospital usage and the antibiotic sensitivity of staphylococci isolated from hospital carriers, but it must be emphasized that our strains were isolated from patients with infections, and there is some doubt that the casual hospital carrier has the same type of staphylococci as those that cause serious staphylococcic infections of the type from which our strains were isolated (Lepper *et al.*[11], Sylvester and Grundy[15]).

An alternate explanation to antibiotic usage as a cause of increasing resistance to antibiotics of the staphylococcus is that in order for the staphylococcus to have achieved its ubiquitous position in the world of bacteria, it must have a tremendous capability of variation and through the years must

be constantly undergoing changes in its biochemical nature. If this is so, drugs that are selected on the basis of a particular biochemical characteristic of staphylococci will eventually always become obsolete because the biochemical characteristic will in the future inevitably change because of the natural variability of the staphylococcus species. This simple explanation which is independent of the factor of antibiotic usage seems to us to be a reasonable one and one that should act as a constant stimulus for the development of new drugs for the treatment of staphylococcic infections.

Summary and Conclusions. One hundred fifty-two instances in which bacterial sensitivity tests were available before and after antibiotics were given to patients were studied. In 53 cases the sensitivity to staphylococci remained the same to the antibiotic that was administered. In 57 cases the second culture was more resistant and in 42 cases it was more sensitive.

In 17 cases in whom a single antibiotic was given, 5 instances of increased resistance were found and in 27 cases where two antibiotics were given simultaneously (to both of which the initial culture was sensitive) 14 instances of increased resistance were observed. Thus, combinations of antibiotics did not appear to affect the subsequent development of the resistance.

Our conclusion is that our data support the concept that the administration of an antibiotic to a patient does not greatly influence the antibiotic sensitivity of staphylococci that are infecting that patient. Therefore, subtle influences other than antibiotic usage must be sought to explain the changing resistances of staphylococci to antibiotics. Furthermore, our data do not show that the giving of combinations of antibiotics prevents increases in antibiotic resistance of staphylococci isolated from infections.

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SUMMARIO IN INTERLINGUA

Le Sensibilitate A Antibioticos In Staphylococcos Isolate Ab Le Mesme Patientes Ante E Post Lor Tractamento Con Antibioticos

Esseva studiate 152 casos in que tests de sensibilitate bacterial ante e post le administration de antibioticos al patientes esseva disponibile. In 53 casos le sensibilitate del staphylococcos con respecto al antibiotico administrate remaneva le mesme. In 57 casos le secunde cultura esseva plus resistente, e in 42 illo esseva plus sensibile.

In un gruppo de 17 casos in que un sol antibiotico esseva administrate, 5 casos de augmento del resistentia esseva trovate, e in un gruppo de 27 casos in que duo antibioticos esseva administrate simultaneemente (ambes con sensibilitate bacterial in le cultura initial), 14 casos de augmento del resistentia esseva observate. Assi, combinationes de antibioticos non pareva afficer le subsequente disveloppamento de resistentia.

Nostre conclusion es que le datos trovate supporta le notion que le administration de antibioticos non exerce un grande influentia super le sensibilitate del staphylococcos que ha inficite patientes particular. Ergo, subtile influentias altere que le uso de antibioticos debe esser cercate pro explicar le alterate resistentia de staphylococcos contra le varie antibioticos. In plus, nostre datos non indica que le administration de combinationes de antibioticos preveni le augmento del resistentia contra le antibioticos in le staphylococcos isolate ab patientes inficite.

PROGRESS
OF
MEDICAL SCIENCE

OPHTHALMOLOGY

UNDER THE CHARGE OF

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MEASUREMENT OF RETINAL ARTERIAL PRESSURE

BY HENRY P. WAGENER, M.D.

SEVERAL years ago, Keith and I[144] noted that, though the type of sphygmomanometer now in use was invented by Riva-Rocci in 1896, it was not until after 1910 that sphygmomanometers were very generally used by practicing physicians. It was about this same time that interest was aroused in devising methods for measuring the pressure in the arteries of the retina. Elschnig[47] stated, in 1911, that it was unfortunate that as yet there was no apparatus available for checking the blood pressure in the central artery of the retina. However, in that year, Rubino[108] stated that Bajardi[10] had constructed in 1905 a mercury manometer type of apparatus by means of which he had estimated the normal retinal arterial pressure to be 49 to 59 mm. Hg diastolic and 58 to 67 mm. Hg systolic. Rubino[108] himself used for his studies of the retinal arterial pressure a Bloch-Verdin[17,18] type of sphygmomanometer modified by Cheron[25] as well as the Bajardi[10] apparatus.

Thomson Henderson[56] had devised in 1914 a modified Geneva lens measure by means of which he estimated that the retinal arterial diastolic pressure varied between 15 and 25 mm. Hg above the intraocular tension. However, it was not until after Bailliart[6] presented his ophthalmodynamometer in 1917 that clinical study of retinal arterial pressure really began. Bailliart[8] stated that Deyl[39] had written in 1912 that a physician accustomed to the use of the ophthalmoscope could learn quite quickly to determine the degree of pressure necessary to make a normal arterial pulsation appear but that he had not been able to construct an apparatus to measure this pressure. Bailliart[8] wrote that he himself had commenced work on his dynamometer in 1909. As noted by Koch[69], varied models of ophthalmodynamometers have been introduced by Baurmann[14], Uyemura and Suganuma[137], Spinelli[123], Sobanski[119], Kukan[74], Keil[64], Linksz[81] and Gutmann[54]. However, the Bailliart instrument has remained the most popular, although Van Allen and Blodi[138]

used Müller's[100] dynamometer in their studies.

There has always been considerable disagreement as to the actual height of the retinal arterial pressure in normal individuals. In 1917, Bailliart[6] using a Bloch-Verdin-Cheron sphygmomanometer gave the figures 67 mm. Hg diastolic and 98 mm. Hg systolic; but, later that same year, using a more sensitive modification of the Bloch-Verdin instrument which he had designed himself, he[6] obtained the values to which he has adhered, with only a slight variation, ever since, 25 to 35 gm. diastolic and 35 to 80 gm. systolic. In 1937, he[8] gave the figures, 35 mm. Hg diastolic and 70 to 80 mm. Hg systolic. He estimated that, normally, the retinal arterial diastolic pressure would be 45% of the brachial diastolic pressure. Magitot and Bailliart[88] assumed that the dynamometer measured the pressure in the branches of the central artery of the retina. The ophthalmodynamometer was calibrated in grams but the directly read figures were converted into mm. Hg by reference to a scale constructed by Magitot and Baillart[88] to take into account varying initial intraocular tensions. Most recent observers in the United States record only the direct readings in grams.

The figures obtained by Bailliart[6,8] for the retinal arterial pressure probably are lower than the actual pressure in these vessels. Priestley Smith[117] in 1918, on theoretic grounds, estimated the mean entrance pressure in the central retinal artery to be 90 to 100 mm. Hg. Again, in 1923, he[118] stated that the arterial entrance pressure into the eye cannot be measured with precision but is estimated to be 40 to 50 mm. Hg diastolic and 70 to 90 systolic. Duke-Elder[43], in 1926, called attention to the fact that the readings obtained by pressure on the eye, as in Bailliart's method, indicate the lateral pressure in the ophthalmic artery and not in the branches of the central retinal artery as claimed by Bailliart[6]. By manometric methods, Duke-Elder[43] obtained the following pressures in the cat: mean pressures, in the carotid 104 mm. Hg, in the ophthalmic artery 99.5 and in the retinal arteries 77.5; systolic pressures, in the ophthalmic artery 119 and in the retinal arteries 80 mm. Hg; diastolic pressures, in the ophthalmic artery 80 mm. Hg and in the retinal arteries 65. Duke-Elder[43] stated: "It would appear, therefore, that the technique elaborated by Bailliart[6] is a fallacious method of estimating the lateral pressure in the ophthalmic artery; and that, whatever clinical value its results may be interpreted to have if considered in this light, merely as figures with a comparative and no absolute significance, they can give no indication whatever of the pressure in the branches of the retinal artery, nor of the relation between the blood pressures in the eye and the intraocular pressure."

Adler[1] agrees with these statements by Duke-Elder[43]. He states that, as pressure on the globe increases venous pressure through obstructing flow of blood from the eye and this spreads back into the arterial side of the circulation, the pressure builds up to the level of that in the main feeding artery, the ophthalmic. He concludes: "On theoretic grounds, therefore, the method is not measuring the pressure in the central artery of the retina, but the level of pressure somewhere between this artery and the ophthalmic artery depending on how rapidly the measurements are taken. . . . The method may have value in affording comparative figures, but it cannot yield exact values on which calculations can be based for physiological purposes, such as determinations of the pressure available for

the formation of aqueous humor." In the United States at present, the ophthalmodynamometer is used largely for comparing the retinal arterial pressure in the two eyes or for comparing the retinal arterial pressure in the same eye before and after surgical procedures on the carotid arteries in the neck. It is universally accepted that the dynamometer measures the pressure in the ophthalmic artery and hence indirectly the pressure in the other intracranial branches of the internal carotid artery.

Koch[70] wrote, "The values for the normal retinal diastolic blood pressure obtained through more than two decades of investigation with the ophthalmodynamometer of Bailliart, range from a low of 18 to a high of 72 mm. Hg, and there is some overlapping with the values for the retinal systolic pressure, since the range for the latter is 36 to 130 mm. Hg." Koch's[69] own values for the diastolic pressure ranged from 20 to 41 mm. Hg, Luo and Ch'en's[84] 32 to 50, Crevasse[32] and his co-workers' 30 to 45. The variable figures obtained by different observers have cast doubt on the accuracy of the dynamometric method. The difference in the lower limits of the diastolic pressure set by individual investigators may depend on whether the examiner records the diastolic pressure at the first visible pulsation or whether he waits for total diastolic collapse (maximal collapsing pulse). According to Friedenwald[52], Fritz[53] considers the interval between these two points to be a measure of the rigidity of the vessel wall.

Streiff and Bischler[125] conducted a study of the accuracy of the ophthalmodynamometric method. In 800 measurements made by the same observer in 200 normal individuals, the maximum error was 4.05 gm. and the mean error, 1.35 gm. in the diastolic pressure and 7.08 gm. maximum and 2.36 gm. mean error in the systolic pressure. The maximum error in the values obtained by two observers in the same normals was 7.35 gm. in the diastolic and 13.4 gm. in the systolic pressures, and the mean error was 2.45 gm. in the diastolic and 4.48 in the systolic pressure. Wood and Toole[150] summed up the situation pretty well when they said that for various reasons it was highly unlikely that, by dynamometry, one could arrive at a figure for pressure in the central artery of the retina that would have any absolute value. They added: "We feel it is neither desirable nor profitable, therefore, to convert the units, nor do we routinely express them as grams. They are, simply, arbitrary units of extraocular pressure, varying in significance from individual to individual but strictly comparable between the two eyes of any one individual. For the same reasons, there is no sharp limit of so-called normal values. Most systolic pressures will fall between 60 and 130, the diastolics between 20 and 70, but values beyond these limits are not abnormal *per se*." It should be noted that the retinal arterial pressures are higher if taken with the patient lying down than they are in the same patient sitting up. Perry and Rose[102] stated that the sitting pressures in their cases averaged 5 mm. Hg lower than the supine.

Magitot[87] wrote in 1922 that it was only the comparison between the local retinal and the general systemic blood pressure that was of clinical value. Such comparison would aid in the detection of increased intracranial pressure and of retinal angiosclerosis. Basing his opinions on Bailliart's[6] work, Lebensohn[79] stated that hypertension in the retinal vessels might be present without any visible changes in their walls, and that it might account for sudden attacks of visual obscuration in apparently healthy persons. It usually

went along with systemic hypertension, but it might be disproportionately elevated as in retinitis of pregnancy or in albuminuric retinitis, or it might precede any other eye findings. He noted that "With increased pressure in the cerebrospinal fluid, the retinal blood pressure is frequently elevated, often without the systemic pressure being changed."

RETINAL ARTERIAL PRESSURE IN SYSTEMIC HYPERTENSION. In 1941, Koch[69] wrote: "Bailliart[6], his co-workers and his followers expressed the opinion that ophthalmodynamometric studies almost invariably are of great clinical importance as a diagnostic aid in the clinical differentiation of types of diffuse vascular disease with hypertension. These investigators claimed that it is entirely possible to detect early pathologic elevations of the systemic blood pressure, to determine the severity or stage of established hypertension and even to recognize the latent, or "prehypertensive," phase. They stated the belief that use of the ophthalmodynamometer by adequately trained persons is a more refined diagnostic procedure than use of the ophthalmoscope by such persons. . . . Since 1924, when Bailliart, Magniel and Saragea[9] concluded from their dynamometric findings in 22 cases of hypertension that elevated, abnormal, relatively disproportionate values probably are found consistently in cases of pathologic elevation of the systemic blood pressure, numerous similar contributions have been made. The retinal diastolic blood pressure in a series of cases studied by Bailliart, Magniel and Saragea[9] ranged from 20 to 120 mm. of mercury, while the systemic diastolic pressure varied from 50 to 180 mm. The percentage ratios ranged from 33 to 96."

Koch[69] studied the caliber of the retinal arterioles and the retinal arterial diastolic pressures in normals, in patients with chronic glomerulonephritis, and in individuals with elevated blood pressure classified into four groups according to the method of Keith, Wagener and Barker[65]. He found that there were definite successive increases in the height of the retinal and brachial diastolic blood pressures as the hypertensive disease became progressively more severe, and that the percentage ratio of the retinal to the brachial diastolic blood pressure also increased progressively. He stated, "Thus, it was found in general that the percentage ratio for the retinal to the brachial blood pressure for all the normal persons, the persons who had chronic glomerulonephritis and the majority of those in hypertension groups 1 and 2, on the basis of individual values, was 55 or less. Conversely, as the hypertensive disease increased in severity, the number of patients who had a ratio of 55% or more progressively increased; on this basis, all the patients in hypertension group 4 exhibited an abnormally high ratio. These values might be thought to indicate that ophthalmodynamometric readings in themselves would be sufficient basis for the classification of elevated blood pressure with reference to the severity of the hypertensive disease." However, Koch[69] concluded that a classification of hypertension on this basis probably was not only impractical but impossible because, while there is a progressive increase in the mean retino-humeral ratio as the hypertension becomes more severe, if the range of the ratios in each group is considered, there is considerable overlapping. He wrote, "Relations between the caliber of the retinal arterioles and the retinal and brachial diastolic pressure are not sufficiently consistent in individual cases to warrant the use of these values in the clinical classification of patients who

have diffuse arteriolar disease with hypertension," and Koch's[70] final conclusion in 1945, after an extensive review of the literature and a re-evaluation of his own studies, was that it was wiser to depend on ophthalmoscopic than on dynamometric findings for estimating the severity of the hypertensive disease in any given individual.

It is quite generally agreed in this country that studies of the retinal arterial pressure are of little value in the management of patients with systemic hypertension. Perry and Rose[102] felt, for instance, that the progressively increasing ratio of retinal to brachial diastolic pressure noted in cases of hypertension is of no real significance because the absolute difference in millimeters of mercury between brachial and retinal arterial pressures is similar in both the normotensive and the hypertensive groups. Foreign observers, however, continue to emphasize the importance of ophthalmodynamometric measurements in patients with cardiovascular renal disease. For example, Suganuma[128] stated in 1937 that, in certain cases of toxemia of pregnancy, the pressure in the central artery of the retina rises disproportionately to the systemic blood pressure. In 1951, De Laet, Hubinont and Blackman[35] noted that a solitary increase in retinal arterial pressure is associated with an abnormal gain in weight as an indication of threatened preeclampsia, and that the retino-humeral ratio rises in most cases of preeclampsia, although, for some unknown reason, in some preeclamptics it falls. And, in 1958, Lijo Pavia[80] called attention to the importance of studying the retinal arterial pressure in pregnant women in whom preeclampsia is suspected. Ardouin, Toulouse and Dubois[3] stated that, in women with hypertensive toxemia of pregnancy,' systematic repetition of comparison of the retinal and humeral diastolic pressures will provide exact information on the evolution of the toxemia, a basis for accurate maternal and fetal prognosis and, after delivery, indication of the subsidence or persistence of the angiospastic process.

At the 1950 International Ophthalmological Congress, both Schiff-Wertheimer[110] and Dubois-Poulsen and Miller[42] supported the thesis that changes in the retino-humeral ratio give an earlier indication of the onset of the malignant phase of hypertension than do ophthalmoscopic changes. In 1955, Miller and Audoueineix[92] expressed the same opinion. They said that the diagnosis was indicated at the same time by ophthalmoscopic and dynamometric findings in 63% of 154 malignant hypertensives, in 58% of 40 potentially malignant hypertensives and in 38% of 13 glomerulonephritics; it was suggested earlier by the ophthalmoscopic findings in 3% of the malignant hypertensive, in 2% of the potentially malignant hypertensives and in 7% of the glomerulonephritics; it was suggested earlier by the dynamometric findings in 34% of the malignant hypertensives, in 40% of the potentially malignant hypertensives and in 55% of the glomerulonephritics. Schiff-Wertheimer[110] noted also that measurement of the retinal arterial pressure may help to distinguish between hypertonic and organic changes in the walls of the retinal arterioles. She thought that relative retinal hypotension indicated a loss of retinal arteriolar tone and might indicate the onset of retinopathy or the imminence of cerebral complications. Bailliart[7] himself, as recently as 1957, concurred with the opinions expressed by Schiff-Wertheimer[110].

Hollenhorst[61] noted that Soto[121], in discussing the importance of ophthalmodynamometry in the study of hypertension, called attention once again to the increased retino-humeral ratio in

patients with hypertension. Bonaccorsi[20] found that the difference between the minimal and the maximal pulsation of the retinal arteries as observed during dynamometry (the index of Fritz[53]) was increased in all of 7 patients with arteriosclerosis, in all of 8 patients with renal disease and hypertension and in 8 of 15 patients with essential hypertension as an indication of changes in the arterial walls. Zahn[154], as noted by Hollenhorst[61], included measurements of the retinal arterial and venous pressures in the evaluation of pharmacologic tests on his hypertensive patients. Matsui[89] observed that a correlation between renal blood flow and retinal blood pressure is present in renal but not in essential hypertension. Such drugs as reserpine and l-hydrazinophthalazine lower systemic and retinal blood pressures and increase renal blood flow, but overdosage may decrease the renal blood flow.

Several observers have studied the effect of anti-hypertensive measures on the retinal arterial pressure. Schiff-Wertheimer[110] stated that sympathectomy for hypertension did not alter the abnormal retino-humeral ratio. Miller and Audoueineix[92] studied the effect of hypotensive drugs on the retinal arterial pressure in 31 cases of hypertension. There was a significant drop in systemic blood pressure in 23 cases; the retino-humeral ratio became lower or normal in 16 but remained high in 7. There was a slight drop in systemic blood pressure in the other 8 cases; the retino-humeral ratio was lowered in 1 but remained high in 7. Stankovic and Plavsic[124] studied the systemic and retinal blood pressures in the reclining, sitting and standing positions after the administration of ganglion-blocking drugs to patients with hypertension. While the systemic pressure always fell, the retinal arterial pressure fell very little and only in the standing position. Miller[91] confirmed these findings, but von Bahr[5] stated that, in his experience, the retinal arterial pressure fell proportionately to the systemic blood pressure after ganglion-blocking drugs in both the reclining and the standing positions.

RETINAL ARTERIAL HYPOTENSION AND OPTIC ATROPHY. According to Koch[70], Lauber[77] and Sobanski[120] each thought that the systemic blood pressure was abnormally low in patients with progressive tabetic optic atrophy, that the retinal arterial diastolic pressure was correspondingly low and that the optic atrophy was caused by local circulatory failure. According to Constantine[29], Lauber[78] and Sobanski[120] believed that the lowest level of retinal arterial diastolic pressure must be at least 14 to 20 mm. Hg higher than the highest normal level of intraocular tension to maintain adequate capillary circulation in the retina and optic nerve. Constantine[29] was not able to confirm the findings of Lauber[77] and Sobanski[120]. She[29] stated: "The final and fundamental point in the theory of Lauber[77] and Sobanski[120] is that the primary optic atrophy is dependent upon a low difference between the retinal diastolic pressure and the intraocular tension. The evidence in this study is directly to the contrary. The mean differential in the normal individuals was 29 mm.; in syphilitics without optic atrophy, it was 34 mm., and in syphilitics with optic atrophy, 36 mm., the highest figure of all. Furthermore, the patients with central nervous system syphilis who had a tryparsamide reaction with involvement of the optic nerves showed a normal differential between the retinal diastolic pressure and the intraocular pressure." Retinal arterial hypotension is present and helpful in the diagnosis of cases of postural hypotension, aortic arch syndrome and pulseless disease.

RETINAL ARTERIAL HYPERTENSION AND INCREASED INTRACRANIAL PRESSURE. Magitot[87] had stated in 1922 that, if the systemic blood pressure is normal, an increase of the diastolic retinobrachial ratio above the normal 0.45 indicates an increase in the cerebrospinal fluid pressure even if papilledema is not present. In 1928, Berens, Smith and Cornwall[16] stated that they had been able to confirm Magitot's[87] observations. They[16] wrote: "In general it may be said, from the experimental and clinical data which we have been able to obtain by the use of Bailliart's ophthalmodynamometer, that in the absence of papilledema, disease of the retinal arteries and general arterial hypertension, a diastolic blood pressure in the central artery of the retina greater by 10 to 15 mm. of mercury than one-half the brachial diastolic pressure, when the patient is sitting or standing, strongly suggests increased pressure in the cerebral arteries, the result of increased intracranial pressure. The exact mechanism which produces this phenomenon, however, is not definitely determined. . . . When papilledema is established, the observations on the retinal blood pressure may be so misleading as to indicate a low intracranial pressure in certain cases when the intracranial pressure actually is high. An explanation is not offered for this phenomenon." Hartman[55] stated in 1949 that the retinal arterial pressure rises in the presence of increased intracranial pressure before the onset of papilledema and drops when papilledema appears.

Luo and Ch'en[84] stated in 1939, "Probably the most important practical application of ophthalmodynamometry is the estimation of the intracranial pressure by determining retinal vascular pressures. When the intracranial pressure is raised experimentally or by disease, the retinal vascular pressure becomes also elevated." However, de Morsier, Monnier and Streiff[99] did not agree entirely with these statements. They found that intracranial tumors were associated more often with normal or low than with high retinal arterial pressures. The concluded that, in a patient with signs of cerebral disturbance but no papilledema, the presence of retinal arterial hypotension, far from ruling out a brain tumor, should on the contrary make it more probable. Baurmann[15] concluded that the retinal arterial pressure was influenced by the intracranial pressure only as a part of the systemic pressure. Koch[70] stated that several observers had examined relatively small groups of patients and concluded that so-called solitary or cephalic arterial hypertension is present in a rather large number of diseases, both systemic and local, which affect intracranial and intraocular pressure relationships. Gutmann[54], for example, was able to demonstrate that abnormally high systolic retinal arterial pressures were present in association with allergies, both clinical and experimentally induced. And Weigelin and his co-authors[149] stated that ophthalmodynamometric measurements were valuable in the study of headaches of undetermined origin. He found that 61.5% of 215 patients showed evidence of a disturbance of intracranial circulation and that his tests could differentiate between vasospastic and vasodilating disturbances. Treatment with the appropriate drugs resulted in more nearly normal response to the tests. The dynamometer did not help, however, in differentiating post-traumatic from idiopathic epilepsy.

According to an abstract in Ophthalmic Literature, Bachstez[4] stated in 1954, "The failure of different methods, many sources of error, formulation of various relations between retinal and brachial blood pressure,

and the lack of pathognomonic findings together with the differences of opinion are confusing and discouraging. After thirty years of work no safe basis for a clinical evaluation of ophthalmodynamometry could be found." Certainly in the light of the recent studies of the retinal arterial pressures in obstructive lesions of the internal carotid arteries, this evaluation will have to be revised.

RETINAL ARTERIAL PRESSURES IN INTERNAL CAROTID OCCLUSIONS. The influence of occlusion of the cervical internal carotid artery on the retinal circulation has been recognized for many years. Elschnig[46] stated, in 1893, that slow and gradual closure of the ophthalmic, internal carotid or common carotid artery is without effect on the circulation in the vessels of the orbit or retina. Sudden closure of one of these arteries can cause momentary changes in the circulation of the retina which will result in transitory disturbance of vision; but no anatomic lesion will follow as the free communication between the branches of the ophthalmic and the external carotid arteries of both sides provides an immediate or rapid return of normal blood volume, blood pressure and rapidity of circulation. If, after thrombosis of the carotid artery, severe ischemic appearances are observed in the retina, it is probable that an embolus from the thrombus has been the cause of the severe retinal involvement. He[47] added, in 1911, that, after ligation of the carotid artery, the pressure difference between the diastolic and the systolic retinal arterial pressure is reduced but that otherwise the circulation is essentially not changed. He did not have an apparatus with which to check the blood pressure, but he noted that there was no change in the caliber of the retinal arteries or veins and that the pulsation in the retinal vessels during finger pressure on the eye seemed to be normal. Rubino[108], one of the earliest users of an ophthalmodynamometer, studied in rabbits the effect on the pressure in the central artery of the retina and in the peripheral portion of the carotid of occlusion of one carotid artery and also the effect of closure of one jugular vein.

The rarity of cases in which the diagnosis of thrombosis of the internal carotid artery was made clinically before the advent of cerebral angiography, probably accounts for the paucity of reports on retinal arterial pressure measurements in these early cases. However, Laignier[75] did report, in 1935, 3 cases of unequal retinal arterial diastolic pressures in the two eyes. In one of these cases, an aplasia of the carotid artery was found on the side of the eye with the lower retinal arterial pressure. In the other cases, there was considerable difference between the pressures in the two carotids. In 1936, Baurmann[15] studied the effects of carotid compression on the retinal arterial pressure as determined by dynamometery. He observed that compression of the homolateral carotid artery caused a definite drop in the retinal arterial pressure, more in the systolic than in the diastolic. He thought that a drop of more than 10 mm. Hg in the diastolic pressure indicated that it would not be safe to ligate the artery. Baurmann[15] observed also that compression of the contralateral carotid artery caused a rise in both the systolic and the diastolic retinal arterial pressures, the amount of the rise furnishing an indication of the efficiency of collateral circulation through the circle of Willis.

The reports by Sjöqvist[116] and by Moniz, Lima and de Lacerda[98] that occlusion or thrombosis of the cervical internal carotid could be demonstrated by angiography aroused interest in the

antemortem diagnosis of these lesions which had been found previously as a rule only at necropsy. However, these demonstrations were not followed immediately by attempts to apply the technique of ophthalmodynamometry to the diagnosis of carotid occlusions. Bailliart[8] did mention in 1938 that, in some cases of hypertension the retinal arterial pressure might be elevated in one eye and normal or low in the other. This he regarded as a valuable sign of obliteration at the origin of the ophthalmic artery, in the central artery of the retina before its passage through the sclera or of the internal carotid artery. But it remained for Krayenbühl and Weber[72] to include actual dynamometric measurements in case reports of internal carotid thrombosis. In 1944, these authors reported their observations in 17 patients who had thrombosis of an internal carotid artery; they had measured the retinal arterial diastolic pressure in 3 cases and found it to be the same in each eye. However, Krayenbühl[71] added several more cases in 1945 and found in one of them that the retinal arterial pressures, especially the systolic, were considerably lower than normal in the eye on the side of the involved carotid. Also in 1944, Trotot[136] reported a case of thrombosis of the left internal carotid confirmed at necropsy; the retinal arterial diastolic pressure was 35 to 40 mm. Hg lower in the left than in the right eye. For the next several years, scattered case reports appeared in the European literature confirming the observation that the retinal arterial pressure was lowered in the eye ipsilateral to an occluded internal carotid artery. Radovici and Lasco[105] reported 2 cases, Schiff-Wertheimer[110] 1 and Weigelin and his associates[149] 6; the value of ophthalmodynamometry in the diagnosis of carotid thrombosis was pointed out by Bronner and Lobstein[22]. Barré and his co-workers[13] had found equal pressures in the two eyes in one case, but the thrombosis of the carotid had occurred 12 years before. In 1946 and again in 1950, Milletti[93,94] listed the features of his so-called tonometric retinal syndrome which he considered to be pathognomonic of unilateral internal carotid occlusion, lower systolic arterial pressure in the ipsilateral eye even if the diastolic pressure is the same in each eye; the arterial pressure is not altered in either eye by compression of the presumed occluded carotid; the arterial pressure is lowered in both eyes, but to a greater degree in the contralateral eye, by compression of the presumably normal carotid. These are accepted today as the characteristic signs of carotid occlusion, but many observers hesitate to compress the normal carotid because of the danger of producing focal cerebral ischemic lesions.

The first report in this country on the application of ophthalmodynamometry to the study of carotid artery occlusions appears to have been made by Drew and Petrohelos in 1951[40]. De Jong[34] called attention to Milletti's[93] findings in 1949, but Sugar, Webster and Gurdjian[129] did not mention dynamometry in 1950. Johnson and Walker[63], in 1951, also called attention to Milletti's[93,94] studies and stated that the retinal arterial pressure had been measured in 7 of the 107 cases of carotid thrombosis that they had collected from the literature; the pressure was lower in the ipsilateral eye in 2 of the 6 cases in which the eyes were compared. They did not mention using the method in any of their own 6 cases. Drew and Petrohelos[40] studied the effect of interruption of the superior cervical sympathetic chain in 2 patients with spontaneous thrombosis of the internal carotid artery. The retinal arterial pressure was lower on the af-

fected side in both cases but rose significantly after the interruption of the sympathetics. Also in 1951, Denny-Brown[37] noted in a case of chronic carotid occlusion a definite difference in the amount of finger pressure required in the two eyes to cause the arteries of the disk and retina to pulsate and blanch. But Fisher[49] stated in 1952 that careful measurement of the retinal arterial pressure had not been made in his cases and that it had been difficult to decide from rough estimates by finger pressure whether the arterial pressures were significantly altered. Ophthalmodynamometry was not mentioned in 1952 by either Poppen and Baird[104] or Schneider and Lemmen[111], and Walsh and Smith[146] stated that they had not had any experience with the method. In 1953, Drew and Petrohelos[41] again called attention to the value of dynamometry in the diagnosis of carotid artery occlusion and to its reliability if the findings are typical. They reported the atypical finding of a systolic pressure too high to be measured in the eye contralateral to the lesion, which proved to be a glioblastoma multiforme of the frontal and parietal lobes. Later the same year, Thomas and Petrohelos[134] described in some detail their findings in 5 cases of proven carotid artery thrombosis and 3 of carotid ligation. In 7 of the 8 cases, the retinal arterial pressure was found to be significantly lower on the side of the occlusion. In one of the cases of carotid thrombosis, the retinal arterial pressure was lower in the contralateral eye; but, in this case, the brachial artery pressure was also lower on that side. These observers found that the difference between the pressures in the two eyes of 50 normal controls ranged from 0 to 15.4% for the diastolic and from 0 to 12.6% for the systolic pressure. In the cases of carotid occlusion, the difference in pressures was much higher, ranging from 0 to 77.5% for the diastolic pressure and from 2.2% to 56.9% for the systolic. These figures would seem to indicate that the drop in pressure was greater in the diastolic and not in the systolic as Milletti[93,94] believed. Thomas and Petrohelos[134] suggested that immediate ligation of the carotid is safe if it lowers the ipsilateral retinal arterial pressure less than 20%; if tentative ligation lowers the pressure between 20% and 50%, gradual occlusion will be safe, but, if it lowers the pressure more than 50%, ligation will not be tolerated. The authors[134] concluded that, "The finding of equal retinal artery pressures does not exclude impairment of the internal carotid blood flow, but, if other reasons for inequality are excluded, unilateral lowering of the retinal artery pressure is strongly suggestive evidence of interference with internal carotid blood flow.

The articles by Drew and Petrohelos[40,41] and Thomas and Petrohelos[134] undoubtedly stimulated the interest of American neurosurgeons, neurologists and ophthalmologists in ophthalmodynamometry. Svien and Karavitis[131] reported, in 1954, a case of spontaneous thrombosis of the right internal carotid artery in which the retinal arterial pressure, both systolic and diastolic, was definitely lower in the right than in the left eye. They commented that they had not had sufficient opportunity as yet to determine whether ophthalmodynamometry would prove to be of value in the diagnosis of such cases. Chambers[23] and Ochs, Sensenbach and Madison[101] and Shapiro and Peyton[113] writing in 1954 did not mention retinal arterial pressure. And Fisher[50] wrote: "The clinical diagnosis of carotid obstruction is often an uncertain one. Carotid arteriography is not justifiable except as part of a research project, so that palpation of the carotid vessels is the only

clinical measure available at present. . . . Comparison of the pressure in the central artery (of the retina) on each side by manual methods has not been of help personally, and there is need for a carefully controlled study of such pressures by instrumental means." Reports of such studies commenced to appear in the literature after 1955.

THE SYMPTOMATOLOGY OF THROMBOSIS OF THE INTERNAL CAROTID ARTERY. As noted by Van Buskirk[140], carotid artery thrombosis can develop in 3 distinct patterns: the apoplectic pattern is followed in from 35% to 70% of cases in different series (29% in Shapiro and Peyton's[113] series); the pattern of transient episodes, so-called "stuttering," in 30% to 40% (59% in Shapiro and Peyton's[113] series); and the pattern of progressive neurologic deficit, simulating brain tumor, in 15% to 25% (12% in Shapiro and Peyton's[113] series). The symptoms of unilateral carotid occlusion are listed by King and Langworthy[66] as loss of vision in the homolateral eye due to closure of the ophthalmic artery with later visible optic atrophy, temporal anopsia in the contralateral eye, contralateral hemiplegia and hemianesthesia and, if the left cortex is involved, aphasia. None of these symptoms or findings are pathognomonic of carotid thrombosis, though, as Van Buskirk[140] comments, monocular blindness with contralateral hemiplegia is almost diagnostic in itself. And it is stated often that certain diagnosis can be made only by angiography or surgical exploration.

Walsh and King[145] stated in 1942 that "Homolateral blindness and primary atrophy of the optic nerve are always present, according to our experience, in cases of thrombosis of the internal carotid artery, while the other signs may vary." The diagnosis of internal carotid artery thrombosis had been made only rarely up to that time. Actually, in larger series collected later, like that of Webster, Gurdjian and Martin[147], optic atrophy has been found to be present in only 3% to 12% of the cases. Homonymous hemianopsia has been reported in from 5 to 27% and unequal pupils, with miosis usually on the side of the lesion, in about 13%. The most frequent ocular disturbance is episodes of transient unilateral blindness which have been reported to occur in from 5 to 30% of the cases. The combination of this complaint with the finding of abnormally low retinal arterial pressure in the affected eye is highly suggestive or confirmatory of the diagnosis of stenosis or occlusion of the internal carotid artery. That permanent blindness does not occur in a higher percentage of these patients is probably due to the rich anastomotic circulation between branches of the external carotid and the ophthalmic artery, which has been demonstrated by Walsh and King[145] and by Francois and Neetens[51].

Reports of single cases, as by Larmande and associates[76], of small groups like that of Dejean and associates[33] and of larger groups like those of Heyman, Karp and Bloor[57] and of Perry and Rose[102] have amply confirmed the diagnostic significance of retinal arterial pressure measurements in occlusive lesions of the internal carotid artery. Differences between the arterial pressures in the two eyes greater than 15% are rare apparently. So, after ophthalmodynamometer studies in patients with neurologic evidences suggesting carotid artery occlusion, in patients with intracranial aneurysms, in cases of carotid ligation and of manual compression of the carotid as well as normal individuals, Heyman, Karp and Bloor[57] concluded that unilateral reduction of 25 to 30% in both systolic and diastolic retinal arterial pressures is diagnostic of impaired carotid circu-

lation. They thought that it was necessary to measure both systolic and diastolic pressures. Perry and Rose[102] examined 37 patients with neurologic vascular disease, 25 of them with hemiplegia of recent origin. In 7 patients, there was a difference of more than 15% between the arterial pressures in the two eyes; all of them had positive angiograms. In 3 of the 7, the arteriogram revealed occlusion of the internal carotid on the side of the lower pressure, and in 2 others it showed marked narrowing of the artery. In 1 of the 7, an angiocardiogram showed a narrow aortic arch and non-filling of the innominate artery. In the other case with unilateral low retinal arterial pressure, the arteriogram showed normal carotid arteries but a homolateral cerebral tumor. Angiograms were negative in 6 cases; arterial pressure differences between the two eyes were less than 15% in all. Spalter[122] studied 10 cases of cervical internal carotid thrombosis, all confirmed by arteriography. Significant differences, ranging from 10 to 85%, between the arterial pressures in the two eyes were present in 9; in the tenth case, the occlusion had occurred 3 years before the examination. In 1 of 2 cases in which the occlusion of the carotid was located distal to the origin of the ophthalmic artery, the retinal arterial pressure was higher in the homolateral eye.

Hollenhorst[58,59,60] called attention to two previously unreported phenomena which he had observed in his series of patients with thrombosis of the internal carotid artery. Cotton-wool patches were present in the retina of the ipsilateral eye in 4 of 38 cases, and hypertensive changes in the retinal arterioles were of lower grade in the ipsilateral eye in 2 patients who had hypertension as well as carotid thrombosis. Similar changes had been observed in cases of carotid ligation by Swan and Raaf[132], by Schenk[109] and by Kirby and Hollenhorst[67]. Fisher[48] stated that unilateral transient blindness was the outstanding premonitory symptom of his cases of carotid thrombosis, and it was noted as the most frequent ocular disturbance in several reported series. Hollenhorst's[58,59,60] findings would suggest that a number of the cases were in the stage of intermittent insufficiency rather than of complete occlusion when the attacks of transient blindness occurred. It has been noted that the transient attacks may cease without permanent loss of vision after complete occlusion of the carotid has developed.

INTERMITTENT INSUFFICIENCY OF THE CAROTID ARTERIAL SYSTEM. This term was used by Millikan and Siekert[95] to designate cases seen during the "stuttering" phase of the development of carotid thrombosis. They stated that, in differentiating intermittent insufficiency of the internal carotid from basilar system insufficiency, "Absence or marked diminution of pulsation of the internal carotid artery or an extensive decrease in retinal blood pressure on the involved side will favor a diagnosis of carotid insufficiency." A committee of the American Medical Association[26], of which Millikan was the chairman, used the term "recurrent focal cerebral ischemic attacks" for the same syndrome. Millikan, Siekert and Whisnant[97] gave the following description: "Patients with the syndrome of intermittent insufficiency of the internal carotid arterial system have intermittent attacks of unilateral impairment of motor (paresis or paralysis) or sensory (numbness or paresthesia) function or both. When the dominant hemisphere is involved, aphasia may occur. About 10% to 15% of the patients have unilateral impairment of vision in the eye homolateral to the artery affected (opposite to the weak extremities). Each attack begins abrupt-

ly and a common duration is 5 to 15 minutes. The patient returns to normal after each episode except when a minor neurological deficit accumulates after a number of attacks. . . . Finally an episode may occur which does not terminate in the usual 5 to 15 minutes but persists and progresses over many minutes or a few hours, 'slow stroke' or 'stroke in evolution.' "

Hollenhorst[60] reported a considerably higher percentage of amaurosis fugax in his series of cases. Thus unilateral amaurosis fugax occurred in 56% and transient homonymous hemianopsia in 2% of 86 carotid insufficiencies as compared to 5% and 3% respectively in 38 cases of carotid thrombosis. On the other hand, permanent organic lesions occurred more frequently in the thrombosis group. Thus, occlusion of the central artery of the retina developed in 16% and permanent homonymous hemianopsia in 16% of the cases of carotid thrombosis and in 9% and 2% respectively of the cases of carotid insufficiency. Unilateral retinopathy was observed in 11 and unequal retinal hypertensive vascular changes in 8 of the cases of intermittent insufficiency.

Hollenhorst[58,60] stated that, if the diastolic retinal arterial pressure was less than 50 gm., he considered a difference of 5 gm. between the two eyes to be significant; if the diastolic pressure was more than 50 gm., then a difference of 10 gm. would be significant. Systolic pressure measurement need not be taken unless the diastolic was found to be essentially normal in a patient strongly suspected of having a unilateral carotid occlusive lesion. If the diastolic pressure is found to be near 20 gm. with the patient seated, it can be raised for greater accuracy by having the patient lie down. Hollenhorst[60] found the retinal arterial pressure significantly lower on the affected side in 70% of 83 cases of carotid insufficiency and in 76% of 33 cases of carotid thrombosis. The pressures in the two eyes were equal in 24% of the insufficiencies and in 21% of the thromboses. The pressure was higher in the eye on the involved side in 6% of the insufficiencies and in 3% of the thromboses. Usually the pressure in the eye on the affected side was about 25 to 50% of that in the other eye.

OPHTHALMODYNAMOMETRIC STUDIES IN CAROTID LIGATIONS. In the early days of the revival of ophthalmodynamometry, neurosurgeons became interested in its possible value in deciding on the safety of ligation of the common or internal carotid artery in individual cases. Svien and Hollenhorst[130] reported that the retinal arterial diastolic pressure was significantly lowered in all of 11 cases in which the internal carotid artery was ligated and that the low pressure was maintained for up to 10 years. Pressure differences between the normal eye and the eye on the side of the ligation ranged from 22 to 71%. Pressure differences between the two eyes followed ligation of the common carotid also, in a range of from 10 to 63%. The patients with pressure differences between the two eyes of 47% and 63% respectively each had additional lowering of the pressure after subsequent ligation of the internal carotid, and the ligature on the internal carotid had to be released as it was not tolerated. The initial drop in pressure after ligation of the common carotid was not well maintained. Hemorrhage recurred from the intracranial aneurysm in 2 patients in whom the retinal arterial pressure returned essentially to normal some months after ligation of the common carotid artery.

Blodi and Van Allen[19] determined that percutaneous digital compression of the cervical carotid system produced an average drop of 50% in the systolic or diastolic retinal arterial pressures or

in both in 9 of 10 cases. The drop in pressure ranged from 25 to 75% systolic and from 12 to 100% diastolic. This percentage drop is in the same range as that reported by Bakay and Sweet[11, 12] from direct pressure readings in the internal carotid artery when the common or internal carotid is occluded proximally. Blodi and Van Allen[19] stated that comparative retinal arterial pressure studies in 3 cases of proven internal carotid artery occlusion revealed that the pressures on the side of the occlusion were lower than those on the contralateral side by 30 to 49% systolic and 27 to 54% diastolic. Two of the cases were subjected to surgery without preliminary angiography; the retinal artery pressures gave substantial and valid support to the clinical diagnosis.

Bakay and Sweet[11,12] found that the percentage fall in systolic pressure upon closure of the common carotid artery in the neck is essentially the same in all of the intracranial branches of the artery as it is in the trunk in the neck immediately distal to the site of closure. Therefore, measurements of the pressure drop in the carotid in the neck proves to be a reliable indication of the fall in pressure throughout the branches of that carotid. Rand[106] demonstrated in 3 cases of ligation of the carotid artery in the neck for bleeding intracranial aneurysms, that the changes in the retinal arterial pressure after the ligation closely paralleled the pressure changes in the internal carotid artery, as determined by direct measurements. Sweet, Sarnoff and Bakay[133] and Voris[141] stated that a fall in pressure after carotid ligation to 30% of the original level in the carotid above the occlusion indicates a hazardously poor collateral circulation. Hollenhorst, Wilbur and Svien[62] concluded from their studies that, if compression of the common or internal carotid artery produces a decrease of 20 to 50% in the retinal arterial diastolic pressure (or a decrease to a level of 30 to 35 gm.), ligation of the compressed carotid will probably be safe, not attended by ischemic sequelae in the central nervous system, and yet probably will be effective in reducing the risk of future rupture of the intracranial aneurysm. If, however, compression causes the retinal arterial pressure to decrease to near zero, and this level persists even after 2 minutes, the danger of complications increases, and the surgeon should be alerted to such hazards.

Sweet, Sarnoff and Bakay[133] stated that the development of focal cerebral lesions after internal carotid occlusion could not be correlated definitely with pressure measurements just distal to the occlusion. Brackett[21] stated that one of his patients developed complications after carotid ligation although the systolic pressure in the carotid had dropped only to 42% and the diastolic to 50% of the previous levels. On the other hand, complications did not develop in a case in which the pressures fell to 25 and 34% of the previous levels. Strobos and Mount[126] thought that the reliability of intracarotid pressure measurements in prophesying complications might be seriously impaired by the occurrence of a fall in general blood pressure or of local spasm after carotid ligation. Heyman, Karp and Bloor[57] stated that they did not think that ophthalmodynamometry could be depended on to determine the extent of the decrease in cerebral circulation following carotid ligation or to predict in which cases ligation would be safe. Van Allen and Blodi[138] were able to demonstrate the value of ophthalmodynamometry in determining the effectiveness of a ligation of a carotid artery. They stated that, "Studies of pressure in the carotid system, direct or indirect, are not as val-

uable as we would desire in predicting the result of proposed carotid ligation. It would seem, however, that the simple method of ophthalmodynamometry may eventually prove to yield as much practical information as direct intracarotid pressure measurements." Lobstein, Philippides and Montreuil[83] stated that measuring the retinal arterial and carotid pressures seemed to be of real value in enabling the surgeon to adjust the ligature of a carotid so as to make it effective in producing a sufficient but not dangerous reduction in cerebral blood flow. They thought that the retinal arterial pressure measurements gave more information on the effectiveness of the ligature and the intra-carotid, on the safety of the ligation.

MECHANISM OF THE TRANSIENT ATTACKS IN OCCLUSIVE LESIONS OF THE CAROTID ARTERIES. The view that recurrent transient episodes of loss of vision or of neurologic deficit might be accounted for by spasms either of the carotid itself or of the smaller intracranial arteries induced by the lesion in the carotid, was supported by Moniz, Lima and de Lacerda[98], by Andrell[2], by Fisher[48,49,50] and by Yates[153]. Wright[152] said that, while the mechanism of transient strokes might be on the basis of vasospasm, "perhaps more often it is due to a combination of atherosclerotic narrowing of the lumen with a temporary sludging of the formed elements of the blood, which then disintegrate and move on to clear the passageway and improve the circulation." Millikan, Siekert and Shick[96] thought that a similar course of events might occur with an early thrombus but that it was more likely that the clot would break off and lodge as an embolus at an arterial branching and then be fragmented and carried away. Knight[68] also thought that the transient attacks might be due to multiple emboli lodging in the small cerebral vessels. The majority of observers seem to favor the concept that temporary drops in the systemic blood pressure produce these episodes either through reducing the adequacy of the collateral circulation or by further reducing the blood flow to an area already relatively ischemic because of atherosclerotic narrowing of the lumen of the nutrient artery. Among the authors favoring this mechanism are Corday and Rothenberg[30], Corday, Rothenberg and Putnam[31], Cloake[27], Edwards and Rob[45], Denny-Brown and Meyer[38], Meyer, Leiderman and Denny-Brown[90], Shanbrom and Levy[112], Wood and Toole[150] and Crevasse, Logue and Hurst[32]. Eastcott, Pickering and Rob[44] stated, however, that, in their patient, the attacks could not be reproduced by induced hypotension.

In the report of the A.M.A. committee on cerebrovascular diseases[26] it is stated: "The mechanism of the recurrent ischemic attack is far from a settled matter. Formerly they were designated as attacks of 'cerebral vasospasm,' and the concept is in agreement with their brevity, repetitiveness, and complete reversibility. However, as yet there is no proof that vasomotor phenomena play any part. As already pointed out, the attacks are closely related to atherosclerosis and thrombosis and usually appear when the local cerebral circulation is about to fail completely with disastrous results. Precipitation of the attacks has been attributed to a transient fall in the systemic blood pressure, although such a fall is usually not detectable at the bedside. It has been shown that anticoagulants abolish the attacks in most cases but it is not clear how this is achieved."

TREATMENT OF OCCLUSIVE DISEASE OF THE CAROTID ARTERY. Various forms of surgery have been recommended for the treatment of occlusive lesions of

the carotid arteries and carried out with varying results. Chao and his coworkers[24] resected the thrombosed segment of the artery in 2 cases. Johnson and Walker[63] stated that excision of the thrombosed segment had been performed in 28 cases with improvement in 7 of the 13 cases in which the results had been reported. Webster, Gurdjian and Martin[147] stated that excision of the thrombosed segment in 41 cases revealed atherosclerosis in all. They suggested arterial grafts for incomplete obstructions. Excision of the occluded segment and reconstruction of the artery was performed by Eastcott, Pickering and Rob[44] and by Edwards and Rob[45], arterial grafts by Denman, Ehni and Duty[36], subclavian-internal carotid shunt by Lyons and Galbraith[85], and thromboendarterectomy by Rob and Wheeler[107], by Strully, Hurwitt and Blankenberg[127], by Wood and Toole[150], by Kuhn[73], by Connell[28] and by Van Allen, Blodi and Brintnall[139].

Good results from the treatment of intermittent insufficiencies of the internal carotid artery with anticoagulants were reported by Siekert, Millikan and Shick[114], by Siekert, Millikan and Whisnant[115], by Wright[151], by McDevitt, Carter, Gatje, Foley and Wright[86] and by Hollenhorst. Hollenhorst[60] stated that 5 of the 6 patients who had amaurosis fugax as their only complaint were placed on anticoagulant therapy and their attacks stopped immediately. The attacks recurred in 2 of the patients when the anticogulants were stopped. Anticoagulant therapy stopped the transient attacks in 37 of 41 cases of intermittent insufficiency of the internal carotid artery (90%); but hemiplegia developed in one patient while on anticoagulants, and in 3 others after the treatment was discontinued. Crevasse, Logue and Hurst[32] commented that, in general, the results of surgery had been discouraging. Promising results had been obtained from anticoagulant therapy. The symptoms of cerebral vascular insufficiency had diminished and the neurologic status had seemed to stabilize. The reason for the effectiveness of this treatment was not entirely clear; it might delay occlusion of a partially obstructed carotid or it might prevent extension of the thrombus into the cranial cavity.

INDICATIONS FOR OPHTHALMODYNAMOMETRY. Van Allen, Blodi and Brintnall[139] stated that ophthalmodynamometry is indicated as a test preliminary to cerebral angiography. As angiography of a patent carotid is hazardous when the other is obstructed, knowledge of a difference in retinal arterial pressures in the two eyes would make the surgeon aware that the carotid system ipsilateral to the lower pressure might be partially or completely occluded. Retinal artery pressure measurements would help also in distinguishing partial from complete occlusion as compression of the affected carotid should cause a further drop in an already lowered pressure if the occlusion is incomplete. The authors[139] thought that ophthalmodynamometry is indicated in following the results of surgery on carotid occlusions and as a guide to the best use of angiography. Hollenhorst[58] stated that, if the retinal arterial pressure is significantly lowered on the suspected side, angiography is rarely used as there is danger of converting carotid insufficiency into carotid thrombosis.

As noted by Kuhn[73], "Modern treatment of each patient developing a 'stroke' rests on the establishment of a precise anatomic diagnosis. . . . It is now clear that a large number of patients developing stroke do so because of the presence of cervical carotid artery disease. In many instances,

these chronic arterial occlusions are surgically remediable and blood flow to the brain can be increased with subsequent clinical improvement of the patient." As stated by Wood and Toole[150] and by Weigelin and his associates[149] as well as other observers, ophthalmodynamometry is indicated in the differential diagnosis of strokes. Wood and Toole[150] wrote that it is a simple method for screening those patients with cerebral vascular symptoms for whom surgery or anticoagulant therapy may be considered. They thought that it is in the stage of intermittent insufficiency "when prompt diagnosis must precede specific therapy and when arteriography should be avoided if possible, that ophthalmodynamometry will prove most useful." Hollenhorst[58] agreed with this statement. In discussing the differential diagnosis of cerebrovascular accidents, Bronner and Lobstein[22] and Philippides, Lobstein and Montrieul[103] stated that, if there is unilateral lowered retinal arterial pressure contralateral to the hemiplegia, the causative lesion is located in the carotid below the origin of the ophthalmic artery. If the retinal arterial pressure is higher contralateral to the hemiplegia, it is probable that the lesion is in the terminal portion of the internal carotid or in one of its principal branches.

Measuring the retinal arterial pressure is requisite in the study of all cases of amaurosis fugax to distinguish between those due to occlusive lesions in the common or internal carotid arteries and those due to local lesions in the retina or to functional causes. Wagener[143] and Hollenhorst[58] pointed out that, in some of these cases, the finding of low pressures in each eye may lead to the diagnosis of the aortic arch syndrome or pulseless disease. Tour and Hoyt[135] called attention to the value of ophthalmodynamometry in checking the results of thromboendarterectomy in cases of the aortic arch syndrome.

As noted previously, ophthalmodynamometric studies are indicated, before, during and after surgery, in cases in which ligation of the common or internal carotid artery is planned for the treatment of a bleeding aneurysm of the circle of Willis.

To the indications for ophthalmodynamometry mentioned previously, Weigelin[148] added its use in cases of hypertension to determine whether the intracranial circulation is affected disproportionately to the height of the blood pressure and to follow the course of the disease and evaluate the effects of treatment. Lobstein[82] said that the role of dynamometry in the study of arterial hypertension is not negligible because it can indicate in a limited number of cases if the cerebral circulation is more or less menaced than would be suggested by the level of the systemic pressure and the state of the fundus. But, he added, to make a definite survival prognosis on this basis alone is not justified in a disease like hypertension in which there are many and diverse serious factors and in which lesions of the cerebral vessels are responsible for death in only a small proportion of cases.

With reference to the significance of retinal arterial pressure measurements in the detection of increased intracranial pressure, Hollenhorst[58] said: "There is no question but that the retinal arterial pressures are elevated—sometimes extremely elevated—in the presence of increased intracranial pressure, and that they are lowered as soon as visible papilledema appears. However, there are possibilities for mistaken diagnosis here which I think almost too treacherous to permit use of the ophthalmodynamometer as a tool for diagnosing increased intracranial

pressure when there is no papilledema. The first of these is occlusive disease of the basilar artery, in which we have found a markedly elevated retinal arterial pressure among more than half the cases; and the second is generalized elevation of blood pressure, which produces an extremely variable retinal arterial pressure."

Summary. What is commonly called retinal arterial pressure is really ophthalmic artery pressure. It is evident then that measurements of this pressure will reflect the levels of pressure in the internal carotid arterial system.

Ophthalmodynamometry is of value to the ophthalmologist in the differential diagnosis of recurrent episodes of transient loss of vision (amaurosis fugax). It is of value to the neurologist in the differential diagnosis of "strokes" and especially in the diagnosis of intermittent insufficiency of the internal carotid arterial system (recurrent focal cerebral ischemic attacks). It is of aid to the vascular surgeon in evaluating the results of procedures for restoring the lumen of a stenosed or occluded carotid artery, and to the neurosurgeon in assessing the effectiveness and safety of ligation of the common or the internal carotid artery.

There is probably need for a reevaluation in this country of the possible usefulness of ophthalmodynamometry in the investigation of cases of systemic vascular hypertension.

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SURGERY

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RECENT ADVANCES IN THE UNDERSTANDING AND TREATMENT OF PANCREATITIS

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THE enigma of the autodestruction of the pancreas by its own enzymes has come under extensive investigation in recent years, both in relation to pathogenesis and methods of therapy. The purpose of this paper is to review the experimental and clinical data upon which current concepts and management of inflammatory disease of the pancreas are based.

I. Pathogenesis of Acute Pancreatitis. The original classic theory of Opie[71] postulating the reflux of bile into the pancreatic duct by virtue of a common channel secondary to an obstruction at the ampulla of Vater has stood the test of time of over one half century. It has become increasingly obvious, however, that the biliary reflux theory can not explain all cases of pancreatitis, that is, those without a common channel. Furthermore a large body of experimental evidence has been collected which demonstrates that a number of factors appear to be involved, probably sequential in nature, in the development of the necrotizing or hemorrhagic form of pancreatitis.

ANATOMICAL CONSIDERATIONS. Mann and Giordano[62] in 1923 were the first to cast doubt on the adequacy of the common channel theory based on anatomical study of 200 necropsies which indicated that a common channel existed in only 3.5% of cases. Since that time a number of similar studies have been carried out to further investigate this problem. In a study of 100 routine necropsy specimens Cameron and Noble[11] found a common channel in 66%. More recently Sterling[95] in a similar series found that although the pancreatic duct joined the common bile duct in 55%, a functioning

common channel involving two-thirds or more of the papilla existed in only 15% of cases. Newman *et al.*[69] injected the common bile duct and pancreatic ducts in 57 necropsy specimens, demonstrated a common channel in 88% radiographically but felt that complete sphincterotomy would entail an extension of the incision in the papilla beyond the wall of the duodenum in two-thirds of the specimens. Howard and Jones[39] using a similar technique demonstrated pancreatic reflux in 54% of 150 specimens. Hicken and McAllister[36] found in 100 operative and postoperative cholangiograms a reflux of injected Diodrast in 87% of cases. Kleitsch[49] injected the pancreatic duct in a series of 48 specimens and demonstrated that the main pancreatic duct entered the duodenum at the ampulla of Vater in 90%, one-third of these having a communication via the accessory pancreatic duct to a patent accessory papilla; and in 10% the main pancreatic duct emptied into the duodenum via the accessory papilla. It may be concluded from these studies that the duct of Wirsung does join the ductus choledochus sufficiently above the ampulla of Vater to form a common channel capable of biliary reflux in 60 to 70% of the population. It does not follow, of course, that all cases of pancreatitis occur in patients with this particular anatomical arrangement.

INTRADUCTAL PRESSURE RELATIONSHIPS. Closely related to the reflux theory of pancreatitis is the question of the pressure relationships in the common and pancreatic ducts, granted the existence of a free communication between the two systems via a common channel. Much of the earlier studies was in relation to the secretory pressure achieved by the liver and pancreas against obstructed ducts, which is unphysiologic and of little value in the understanding of the fluid dynamics of the biliary pancreatic ductal system. Parry and associates[72] have developed a technique allowing study of these relationships in anesthetized dogs using separate polyvinyl tubes in the common bile duct, pancreatic duct and duodenum, and not interfering with sphincteric function. They found that during fasting the average pressure in the pancreatic duct was about twice that in the common bile duct (91 mm. vs. 48 mm. of water). After a meal, pressures in both ducts rose, that in the common duct only occasionally exceeding that of the pancreatic duct. The maximum pressures were found to be between 109 and 198 mm. of water in the pancreatic duct and between 87 and 178 mm. of water in the common bile duct.

Menguy and associates[64,66], working in the same laboratory and using the same technique, have shown that in cholecystectomized animals biliary pressures were labile and sometimes exceeded pancreatic pressures, which if true in man would be of significance in the patient with a nonfunctioning gallbladder or following cholecystectomy. Also of interest was the demonstration that introduction of alcohol into the duodenum caused a sustained rise in pressure in the pancreatic duct, in view of the clinical association between alcoholism and pancreatitis.

Jordan and Hallenbeck[44] have shown that if the pancreatic duct was completely obstructed pancreatic secretory pressure rises rapidly to as much as 440 mm. of water, then subsides slowly. Wulsin and Siler[104] created external pancreatic fistulae in dogs, found pressures in the unanesthetized dogs as high as 825 mm. of water with an average of 450 mm. of water. They believe that variations in pancreatic secretory pressure is controlled by a double process of secretion and resorption.

DuVal[23] studied pancreatic duct pressures in 4 patients with cutaneous pancreatic fistula and in 9 patients who had undergone retrograde pancreaticojejunostomy for chronic pancreatitis. The resting pancreatic duct pressures in the control group demonstrated a mean of 103 mm. of water and in the chronic pancreatitis group 283 mm. of water. By perfusion studies the pressure necessary to cause decompression into the duodenum was found to be 176 mm. of water in controls and 412 mm. of water in the group with chronic pancreatitis. This indicates the high ductal pressures maintained by the pancreas in response to partial obstruction to the outflow tract encountered in chronic pancreatitis.

It is apparent from these studies that the pancreas maintains considerably higher ductal pressures than does the biliary tract under both resting circumstances and in response to physiologic stimuli. Further studies indicated that this relationship may be occasionally reversed in the absence of a functioning gallbladder. Indeed it would seem that such a reversal could take place following the forceful contraction of a normal gallbladder. Whether such pressure relationships allow the reflux of bile into the pancreatic duct under normal or abnormal conditions has not been completely answered. Most of the evidence available is indirect and would seem to indicate that given proper anatomic and physiologic conditions, such a reflux could occur.

THE EFFECT OF BILE ON THE PANCREAS. The injection of bile into the pancreatic duct at high pressures has been the classic method of producing experimental acute pancreatitis since first used by Claude Bernard. Rich and Duff[88] showed that pressures used in such techniques were unphysiologic and cause the mechanical rupture of ducts with extravasation of bile into pancreatic parenchyma. Fisher and associates[30] have shown clearly that the infusion of bile into the pancreatic duct at low pressures does not cause pancreatitis.

Powers, Brown and Stein[79,93] anastomosed the pancreatic duct to the common bile duct in dogs, then caused repeated attacks of pancreatitis over a 5-month period by causing spasm of the sphincter of Oddi by injection of morphine. Examination of the pancreases showed marked interstitial fibrosis with dilatation and deposition of bile pigments in the ducts. They also found a high concentration of trypsin in the gallbladder bile and concluded that the pancreatitis was due to the activation of trypsinogen within the pancreatic ducts by trypsin. Elliott and coworkers[27] infused the pancreatic duct with bile at 400 mm. of water and found that the pancreas resists infiltration by normal bile and no significant pancreatitis resulted. If, however, bile was inoculated with pancreatic juice of high enzyme content for 12 to 48 hours before infusion, then large amounts (18 to 30 ml. in 30 minutes) entered the pancreas and fatal hemorrhagic pancreatitis resulted uniformly. Incubation of bile with individual solutions of trypsin duplicated the results although a simple mixture of bile and trypsin produced only moderate nonfatal pancreatitis.

In a further study[26] these authors similarly infused solutions of bile salts and trypsin, individually and in combination, and showed that 75,000 units of trypsin resulted in a mortality of 8%, a 4% solution of bile salts resulted in a mortality of 25%, whereas a solution containing bile salts 4% and trypsin 75,000 units produced a mortality of 93%. This work throws a new light on the problem and would appear to answer many of the objections to the

concept of bile as a casual factor in pancreatitis.

OBSTRUCTION OF PANCREATIC DUCT. It has been repeatedly demonstrated that simple obstruction of the pancreatic duct followed by stimulation of secretin will result in varying degrees of pancreatitis. Popper and Necheles[77] produced pancreatic edema after partially ligating the pancreatic duct in dogs, then stimulating the pancreas with secretin. Lium and Maddock[54] ligated the pancreatic duct in cats, stimulated the pancreas with secretin, pilocarpine and mecholyl producing pancreatic changes varying from edema to focal necrosis. Rich and Duff[88] reported earlier a series of 24 cases of fatal hemorrhagic pancreatitis in which they demonstrated epithelial metaplasia in 54% and felt that the partial obstruction of the pancreatic ducts was followed by distention and rupture with extravasation of pancreatic juice into the parenchyma. It is to be noted, however, that these experimental studies have not resulted in diffuse hemorrhagic necrosis and subsequent investigations have indicated that other factors are necessary for this catastrophe to supervene.

THE ROLE OF TRYPSIN. Basic to the problem of the pathogenesis of pancreatitis is the question of the active agent responsible for the necrosis and other inflammatory changes characteristic of this disease. In that this peculiar type of pathologic picture is encountered only in the pancreas and since experimental pancreatitis produced a number of different agents and techniques lead to the same result, it is logical to look to the pancreatic enzymes as the common denominator. Throughout the past 40 years evidence has been accumulating which would indict the pancreatic proteolytic enzymes, especially trypsin, in this role. Opie[71] was the first to suggest that trypsinogen was activated to trypsin within the pancreas and that this powerful proteolytic ferment attacked the parenchyma of the gland. Rich and Duff[88] produced acute pancreatitis by the intraductal injection of trypsin. They also demonstrated a constant and specific vascular lesion in the pancreas consisting of medial necrosis of arteries and veins in both experimental preparations and necropsy cases which they concluded was due to action of trypsin on vessel walls. They further reproduced this lesion by the subcutaneous injection of a solution of crystalline trypsin and demonstrated the characteristic vascular changes in the vessels in the area of injection. Hara and associates[35] produced fatal hemorrhagic pancreatitis in dogs by injection of a solution of crystalline trypsin into the pancreatic duct under high pressure after eliminating any bacterial factor by pretreatment with antibiotics. Keith and associates[47] produced acute hemorrhagic pancreatitis in dogs by obstructing the pancreatic duct and injecting trypsin interstitially into the pancreas, whereas injection of trypsinogen interstitially in the presence of duct obstruction failed to produce any significant pancreatic inflammation.

Although these studies show that severe pancreatitis can be produced by the injection of solutions of trypsin into the pancreatic duct or parenchyma, the mechanism by which trypsinogen may be activated to trypsin within the ductal system has been less clear. Recent investigations suggest that there may be a number of different processes by which this may be brought about. The work of Elliott and associates[26,27] referred to above, indicates that bile, if allowed to incubate with pancreatic juice, activates trypsinogen to trypsin which in turn may attack the mucoproteins in bile thus eliminating their normally protective action.

Stein and coworkers[79,93] have offered evidence of veno-interstitial and ducto-interstitial pathways whereby circulating blood trypsin may gain access to the pancreas, which in the presence of duct obstruction results in acute pancreatitis by the autocatalytic action of trypsin activating trypsinogen. They produced acute hemorrhagic pancreatitis by pancreatic duct ligation and 24 hours later injected small amounts of trypsin into either the pancreaticoduodenal artery or the saphenous vein. This also could be brought about by producing splenic infarction thus creating a source of circulating trypsin liberated from the necrotic tissue. In this connection, it has been previously demonstrated that other pancreatic enzymes, amylase and lipase, gain passage from the acinar cells to the blood stream, representing a degree of "endocrine" secretion of an essentially exocrine substance[42]. In the presence of ductal obstruction the transfer of pancreatic enzymes to the interstitial and intravascular fluid system is markedly increased. Gibbs and Ivy[33] showed that serum enzymes rise following obstruction of the pancreatic duct, even when the ductal pressure is below the maximum secretory pressure of the pancreas. It is reasonable to assume the trypsin also may enter the blood stream under such circumstances. It has been difficult to prove this in that blood contains a similar proteolytic enzyme, plasmin, present mainly in an inactive form, plasminogen[92] both forms of which rise in concentration in the blood stream after surgical stress[67], and following experimentally produced acute pancreatitis[9].

Hosie and Ziffren[38] have given evidence to suggest that a previously undescribed component of pancreatic juice, the enzyme collagenase, having reached the interstitial space following rupture of the pancreatic duct, acts on the pancreatic parenchyma to produce a product which activates trypsinogen to trypsin.

Thus it would seem that a number of possible mechanisms may be available for the conversion of trypsinogen to trypsin within the substance of the pancreas, this being the crucial factor in the chain of events leading to the dissolution of the organ.

VASCULAR FACTORS. It has become increasingly apparent that an additional factor, that of pancreatic ischemia, is involved in the pathogenesis of hemorrhagic and necrotizing forms of pancreatitis. There is considerable evidence to indicate that the ischemia is due to the action of trypsin, which having gained access to the interstitial spaces, attacks the small arteries and veins causing profound vasospasm and thromboses. The resulting ischemic or infarcted tissue is then even more vulnerable to the digestive action of trypsin. The changes in the vasculature of the pancreas demonstrated by Rich and Duff[88] in fatal cases of hemorrhagic pancreatitis and in experimental preparations supports this concept. Popper and associates[78] showed that ligation of the pancreatic duct and stimulation of the gland with secretin resulted only in pancreatic edema but if ischemia was superimposed by clamping the pancreatic artery for 15 minutes changes ranging from mild fat necrosis to severe hemorrhagic and necrotizing pancreatitis resulted. Ischemia produced in the absence of pancreatic edema did not result in necrosis. Block *et al.*[6] carried out similar studies in rats and found that pancreatic necrosis resulted only if duct obstruction was followed by varying degrees of ischemia.

Pfeffer *et al.*[76] produced acute hemorrhagic pancreatitis in dogs by means of a closed duodenal loop, eliminating the bile factor by ligating the common

duct. They demonstrated vascular changes in the pancreas progressing from congestion and edema to focal hemorrhages at 4 hours to frank hemorrhagic extravasation and parenchymal necrosis at 9 hours.

Thal[99] has investigated the mechanism by which bile injected into the pancreatic duct at high pressures produces pancreatitis. He showed by transillumination studies that bile gaining access to the interstitial spaces following rupture of ductules produces marked segmental vasospasm, especially in the veins, followed by almost complete venous stagnation and finally rupture of capillaries and venules with extensive hemorrhage. Menguy and associates[65] demonstrated that vascular disturbances alone brought about by ligation of pancreatic arteries or veins did not induce acute pancreatitis, but if combined with duct obstruction in recently fed dogs resulted in more severe degrees of pancreatic necrosis. Adams and Musselman[1], however, showed that acute hemorrhagic pancreatitis could be produced by inducing thrombosis of the pancreatic vein with thrombin, in the absence of duct obstruction.

Finally, Probstein and associates[82] have reported 12 cases of atheromatous embolizations occluding in pancreatic arteries found at necropsy, in 10 of which was found associated acute pancreatitis. They feel that the emboli cause an arteritis and adjacent parenchymatous reaction with resultant release of enzymes and spreading pancreatitis.

It may be concluded from these studies that vascular factors play a crucial role in the pathogenesis of pancreatitis and determine whether the process is limited to the stage of edema or progresses to complete pancreatic necrosis. Most of the evidence would indicate that the ischemia following small vessel thromboses add the final insult to an already damaged gland rather than initiating the inflammatory process.

II. Recent Contributions in Relation to the Management of Acute Pancreatitis. ANTITRYPTIC AGENTS AND THE USE OF SERUM ALBUMIN. The isolation of a crystalline protein material from soybeans having an antitryptic activity by Kunitz[50] in 1945 suggested the use of this material clinically in acute pancreatitis. Rush and Cliffton[92] treated experimentally induced pancreatitis in dogs with soy bean inhibitor and found that whereas control animals developed deep shock with elevation in proteolytic titer and sharp fall in serum antiproteolytic activity, treated animals showed stable blood pressure with proteolytic and antiproteolytic activity of the serum maintained at normal levels. Hoffman and associates[37], however, carried out similar studies in dogs and could demonstrate no antitryptic effect or improvement in mortality. Coffee and associates[14] found that the antitryptic index could be elevated by the use of soybean inhibitor and would protect small animals against toxic doses of trypsin as well as modify experimentally produced pancreatic peritonitis.

In 1953 Kenwell and Wels[48] reported favorably on the use of salt-free human serum albumin in patients based on the presence of an antitryptic factor in serum albumin. They treated 11 patients with acute pancreatitis confirmed at operation with 300 to 500 ml. of serum albumin daily for 3 to 5 days and gained the impression that they followed a more benign clinical course. Elliott[24], however, has studied the effect of concentrated serum albumin in dogs with experimental pancreatitis and shown by measurement of antifibrinolysin titers, fibrinogen levels and blood volume determina-

tions that there was no evidence of antitryptic activity of serum albumin but rather its beneficial effects were in the improvement in plasma volume. Elliott and associates[28] also used serum albumin in patients with acute pancreatitis and found an increase in plasma volume and an associated fall in antifibrinolysin titer and fibrinogen levels which were attributed to hemodilution. Elliott[25] has also carried out blood volume studies in patients with acute pancreatitis and found striking blood volume deficits in the range of 1500 ml. He has also treated an additional 28 patients with severe acute pancreatitis with concentrated serum albumin with a zero mortality compared with a mortality of 13% in a control group. It would seem clear from these studies that although albumin therapy is valuable in the treatment of acute pancreatitis, its action is in the correction of plasma volume deficits rather than as a trypsin inhibitor.

THE ROLE OF BACTERIA AND ANTIBIOTICS. Only occasional reports of bacterial studies in clinical pancreatitis are available and these have covered a wide range of species of bacteria. Recent experimental studies, however, would implicate the coliform and clostridial organisms as capable of producing pancreatic necrosis[74,98]. Persky and associates[74] demonstrated a high incidence of clostridia in the peritoneal fluid and portal vein blood in dogs dying of hemorrhagic pancreatitis. They further showed that the mortality could be cut from 100% to 40% by the prophylactic use of polyvalent gas gangrene antitoxin. This same group of authors[98] by differential studies with various antibiotics concluded that other Gram-negative organisms are also involved acting either independently or synergistically.

Thal and associates[101] carried out studies with a number of bacteria and determined that the only microorganisms capable of producing pancreatic necrosis were those which would produce an extensive necrotizing lesion if injected intradermally. They further showed that duct obstruction was essential for the growth and dissemination of such bacteria. By injecting a culture of *Escherichia coli* into the pancreatic duct of dogs followed by ligation of the duct they were able to produce pancreatic necrosis and showed that the necrosis was due to prolonged ischemia due to thrombosis of small vessels. Similar experiments using hemolytic Streptococcus, *Proteus vulgaris, Aerobacter aerogenes* and *Pseudomonas aeruginosa* resulted only in interstitial pancreatitis.

Thal and Brockney[100] have also demonstrated that acute necrotizing pancreatitis may be produced by sensitizing the pancreas to various bacteria and provoking the Schwartzman reaction by the intravenous injection of the endotoxin of the bacteria used, this resulting in extensive capillary and venular thrombosis.

A number of antibiotics have been studied relative to their effect in reducing mortality in experimental pancreatitis as well as the concentration in pancreatic juice. Improved survival rates as compared to controls have been demonstrated with the use of penicillin[53] streptomycin[53] aureomycin[74] and neomycin[98] in experimentally produced pancreatitis using the bile injection technique. Of these aureomycin was the most effective, reducing the mortality from 90% to nearly zero if given orally several days before and after the induction of pancreatitis but resulted in only a 40% survival if limited to parenteral administration[74] indicating that the intestine is the major source for bacteria which invade the tissues after the onset of pancreatitis. Howard, Pulaski and Fusillo[40]

studied the concentration of various antibacterial agents when administered parenterally in pancreatic juice obtained from pancreatic fistulae in patients. They found that sodium sulfadiazine was secreted in pancreatic juice at approximately serum concentration, penicillin in low but therapeutically effective concentrations, streptomycin in ineffective concentration and aureomycin, terramycin and chloramphenicol with no detectible antimicrobial activity. Gerber and associates[32] in a similar study found that erythromycin was secreted in therapeutic concentrations in pancreatic juice and is active at the pH of pancreatic juice. Preston and associates[80] also studied the secretion of antibiotics in pancreatic fluid in a patient with a pancreatic fistula and found that erythromycin and oleandomycin appeared in pancreatic juice following intravenous administration in therapeutic concentrations, whereas sigmamycin and tetracycline could not be detected.

From these studies it would seem clear that bacterial invasion plays an important role in development of pancreatitis and that this factor should be attacked vigorously by utilizing those antibiotic agents therapeutically effective against the pathogens of the gastrointestinal tract.

ADRENAL CORTICOIDS IN ACUTE PANCREATITIS. The anti-inflammatory and anti-shock actions of the adrenal corticoids have led a number of investigators to use these substances in the management of acute pancreatitis clinically and to study the effects on experimental pancreatitis. A number of case reports have appeared in the literature indicating beneficial and often dramatic response to these agents in acute pancreatitis[3,7,10,29,46,91,94]. The exact mechanism by which this effect is achieved is not clear. Anderson and associates[3] produced severe pancreatitis in dogs resulting in 90% mortality in control animals, 40% mortality in those receiving adrenocorticosteroids, 33% mortality in those receiving antibiotics (penicillin and streptomycin) alone, and 20% mortality in those treated with both antibiotics and adrenocorticosteroids. Stewart, Elliott and Zollinger[96] in a similar study found a reduction in mortality from 100% in controls to 48% in dogs treated with cortisone acetate, but a survival rate of 100% was achieved by using intravenous serum albumin therapy. They also found that cortisone did not enhance the effect of serum albumin. They did note a significant reduction in ascitic fluid and pancreatic edema during the first few days of therapy in those animals treated with cortisone.

Dreiling and associates[21] have studied the effect of ACTH, hydrocortisone and prednisolone in patients with and without pancreatitis and found a depression in the volume flow, rate of bicarbonate secretion and rate of amylase secretion of pancreatic juice.

There have also been a number of studies which indicate that adrenal corticoids may have deleterious effects on the pancreas. Stumpf and Wilens[97] have reported focal acinar degeneration, concretions in ductules, and mixed inflammatory reaction in the pancreas of rabbits treated with cortisone. Lazarus and Benscome[52] in a similar study reported pancreatic periductal fibrosis and duct hyperplasia but no necrosis, this effect varying with the length of therapy. Carone and Liebow[12] found postmortem changes in the pancreas of 28.5% of 54 patients who had received ACTH or other adrenal steroids in treatment of diseases other than those of the pancreas. These changes consisted of acinar ectasia, interstitial edema or peripancreatic fat necrosis; only 3.7% of similar lesions being found in a control series of pa-

tients having similar diseases and falling within the same age group. Barr and Wolff[5] have reported 2 cases of hemorrhagic pancreatitis in children following cortisone therapy for asthma and prednisolone therapy for dermatomyositis, respectively. Kaplan[46] has cited evidence that experimental pancreatitis can be induced by the administration of DOCA or the mineralosteroids and states that this effect can be prevented by the simultaneous administration of a glucocorticoid, cortisone. He feels that in acute pancreatitis there is an excess liberation of mineralo-corticosteroids, the deleterious effect of which on the pancreas can be prevented by the use of cortisone.

In a previously unpublished study the authors[31] produced acute hemorrhagic pancreatitis in dogs by injecting a solution of crystalline trypsin into the pancreatic duct and determining the effect of adrenal corticoids on mortality, survival time, serum amylase, white blood count, and pathologic findings. In 24 control animals there was a mortality of 75% and an average survival time of 2.6 days in fatal cases. In a group of 8 animals treated postoperatively with cortisone acetate* 1 mg. per kg. intramuscularly daily for 5 days, the mortality was 12.5% and the one animal that died survived 24 hours. In a second group of animals treated postoperatively with hydrocortisone† 1 mg. per kg. intravenously for 5 days, the mortality was 25% and the average survival time was 7 days. In a third group of 8 animals treated with prednisolone phosphate* postoperatively 1 mg. per kg. intramuscularly for 5 days, the mortality was 12.5% and the average survival time was 6 days. No significant difference was found between treated and control animals as to serum amylase, white blood count, gross or microscopic pathologic findings.

It is concluded that the adrenal corticoids offer protection in acute pancreatitis in terms of decreased mortality. This is probably due to an increased ability of the individual to withstand the stress and shock resulting from an abdominal insult and from some lessening of the inflammatory process in the pancreas. It is felt that the experimental and clinical evidence available recommend the continued use of the adrenal corticosteroids on a short term basis in acute pancreatitis, particularly in the hemorrhagic necrotizing form.

III. Recent Advances in the Surgical Management of Chronic Pancreatitis. The problem of the surgical management of chronic pancreatitis has been extensively studied in recent years utilizing different techniques designed to correct one or more of the known factors involved in the pathogenesis of the acute form of the disease. This is based on the concept that chronic pancreatitis is the end product of a series of bouts of acute inflammation of the pancreas, and that correction of those defects amenable to surgical attack will prevent progression of the disease process.

SURGERY OF THE BILIARY TRACT. *Cholecystectomy and Choledochotomy.* The effectiveness of surgical attack on the biliary tract will depend on whether disease of this system is involved in the genesis of an associated pancreatitis. It has been recognized that pancreatitis may exist in the absence of biliary disease, particularly when related to alcoholism. Kaden and Howard[45] in a study of 100 patients

*The cortisone acetate and prednisolone phosphate were supplied by Merck, Sharp and Dohme.

†The hydrocortisone was supplied by the Upjohn Company.

with acute pancreatitis found that 41% had associated cholelithiasis, whereas 59% had a normal gallbladder. Chronic alcoholism was found in 3% of those with cholelithiasis and in 37% of those in the normal gallbladder group. The incidence of recurrent pancreatitis was 47% in patients with cholelithiasis who were left untreated but dropped to 7% following definitive biliary surgery. The incidence of recurrent pancreatitis in the normal gallbladder group without treatment was 43% and in those having some form of biliary surgery remained at 33%. Raker and Bartlett[85] in a similar study of 83 definitive patients surviving one or more attacks of acute pancreatitis found an incidence of recurrent abdominal symptoms of 31% in the untreated group; whereas those undergoing cholecystectomy and choledochostomy had a recurrence rate of 8%. Thus it may be concluded that excellent results may be expected from removal of the diseased gallbladder and calculi from the common bile duct in preventing the development of chronic pancreatitis, but little benefit will accrue by attacking these structures in the absence of demonstrable disease.

Biliary Diversion. Priestley and associates[81] have reported their results with external and internal biliary drainage in the treatment of chronic pancreatitis. Of 72 patients in which external T-tube biliary drainage was established, 33 were found to have no disease of the biliary tract and in this group 40% obtained complete symptomatic relief; in 39 patients biliary disease was found and complete symptomatic relief was obtained in 62%. Of 28 patients in which internal biliary drainage, mostly by side to side choledochoduodenostomy was established, 16 were found to have no biliary disease of which 31% obtained complete symptomatic relief, and in 12 patients in which biliary disease was found, 50% obtained complete symptomatic relief. No statement was made, however, as to whether the gallbladder was removed in these patients.

Bowers[8] reported 6 cases of chronic pancreatitis created by Roux-Y choledochojejunostomy. Four of these had either concomitant or previous cholecystectomy. All had had good symptomatic relief for a period of 1 to 3 years. Partington[73] utilized Roux-Y choledochojejunostomy in 2 cases with chronic pancreatitis who had had previous cholecystectomy and reported good results. Allbritten[2] reported a single case treated by cholecystectomy and Roux-Y choledochojejunostomy with freedom from symptoms for 3 years. Cholecystojejunostomy, utilizing the Roux-Y technique has been used by Partington with success in 5 patients with chronic pancreatitis. Allbritten reported a similar case which, although complicated by symptoms of cholangitis, ultimately was completely relieved of symptoms.

Sphincterotomy. The relief of obstruction of the ampulla of Vater with consequent reflux of bile into the pancreatic duct by sphinterotomy was first proposed by Archibald in 1919[4]. He believed that "preventing a rise of pressure in the biliary system for a long time, or permanently, would be best secured by cutting the common duct sphincter." The procedure is now widely used due to its re-emphasis by Doubilet and Mulholland. Their early experience was with endodochal sphincterotomy by means of an especially constructed sphinterotome[17,18,19]. They currently perform transduodenal sphincterotomy and have now been able to report 319 sphincterotomies with demonstration of a common channel in 316 of these cases. An operative mortality of 5.3% was reported. Of 190 cases with a minimum

of 2-year follow-up, 169 or 88% obtained complete symptomatic relief and weight gain[11].

Other authors have reported varying results with sphincterotomy in chronic pancreatitis. Priestley[81] reported that of 15 patients so treated, complete symptomatic relief was obtained in 7. Major and Ottenheimer[58] obtained good results in 20 out of 23 patients. Longmire and Briggs[55], however, were successful in only 3 of 8 patients treated by sphincterotomy.

In attempts to improve the results by modifying the usual transduodenal incisional sphincterotomy, Gillette[34] has used "external sphincterotomy" which he describes as a Ramstedt-like incision of an hypertrophied sphincter without entering the duodenal or ductal mucosa. He reported 5 patients successfully treated in this manner. Jones and Smith[43] have utilized transduodenal excision of part of the circumference of the sphincter to create a "wide trough-like stoma," obtaining good results in 5 patients so treated.

It should be pointed out that sphincterotomy can only be expected to be successful in cases where a common channel exists and will not be effective in cases having primary pancreatic duct obstruction. It may be concluded that sphincterotomy has a valuable role to play in that group of patients with chronic relapsing pancreatitis who have a common channel, but for that group who do not have such an anatomical arrangement some other form of surgical attack will have to be considered.

Sympathectomy. The relief of pain in chronic pancreatitis by sympathetic denervation thus interrupting the visceral afferent fibers from the pancreas was first proposed by Mallet-Guy[61]. He has reported a series of 52 resections of the left splanchnic nerve for chronic pancreatitis with 83% satisfactory results[59,60]. Ray and Neill[86] have reported a study on the abdominal visceral sensation in man in which they showed that the pancreas has a bilateral afferent innervation through the splanchnic nerves and the 7th thoracic through the 3rd lumbar sympathetic ganglia. Ogle and French[70] have reported 4 cases of chronic relapsing pancreatitis in which they performed bilateral splanchnicectomy and resection of the sympathetic ganglia from T_8 to L_1 with complete relief of pain for a period ranging from 1 to 6 years.

Rack and Elkins[84] reported 3 patients treated by bilateral resection of greater, lesser, and least splanchnic nerves with resection of the sympathetic ganglia from T_{10} to L_1. They recorded abolition of pain in all 3 patients despite persistently elevated postoperative serum amylase levels in 2 patients and concluded that the operation has no direct effect on the pancreatitis. deTakats and associates[16] have utilized preoperative paravertebral block in determining the side on which to perform sympathectomy and splanchnicectomy. Other authors[41,68,75] have reported successful control of pain by performing resections of the sympathetic innervation of the pancreas on the side on which the pain is manifest. Rienhoff and Baker[90] reported a case of severe chronic pancreatitis in which they first performed left sympathectomy as well as bilateral vagotomy with partial relief of pain but complete relief was obtained only after subsequent right sympathectomy.

Yoshioka and Wakabayashi[105] have performed section of the post-ganglionic fibers of the celiac ganglion supplying the pancreas in 36 patients with excellent results in 35. They state that this procedure allows a more complete denervation of the pancreas than splanchnicectomy or sympathetic ganglionectomy and avoids the excessive

denervation of abdominal organs produced by celiac ganglionectomy.

The role of sympathectomy in the management of chronic pancreatitis has not yet been defined. It would appear to be of greatest value in controlling pain in those cases in which the disease continues to progress despite more definitive measures.

Vagotomy. Vagotomy has been proposed for the treatment of chronic pancreatitis by McCleery and associates[63], on the basis of (1) prevention of ampullary and pancreatic duct spasm of psychogenic origin, (2) prevention of increased pancreatic enzyme production of psychogenic origin, (3) decreased enzyme production resulting from the presence of peptones and hydrochloric acid in the duodenum, and (4) prevention of increased hydrochloric acid production by the stomach in response to emotional stimuli. They reported subdiaphragmatic vagotomy performed on 11 patients with definite improvement in all. They were impressed by the frequency of inadequate personality and emotional instability in this group of patients. Rack and Elkins[84], however, reported 2 cases of chronic pancreatitis on whom they performed bilateral subdiaphragmatic vagotomy without relief of abdominal pain.

Gastrectomy. Gastrectomy as a definitive treatment for chronic pancreatitis has been proposed by Richman and Colp[89]. They feel that good results may be obtained from diversion of acid chyme and food from the duodenal mucosa, thus decreasing secretin stimulation of the pancreas. They have reported a case of chronic recurrent pancreatitis of 14 years' duration with subsequent development of gastric ulcer. Subtotal gastrectomy was performed following which there was dramatic disappearance of pain, steatorrhea and creatorrhea.

Comfort and associates[15] have reported 2 cases of chronic pancreatitis similarly treated with symptomatic relief in one but failure to control abdominal pain in the other.

Pancreatico-jejunostomy. Decompression of the pancreatic ductal system by distal pancreatectomy and pancreatico-jejunostomy allowing the retrograde flow of pancreatic juice into a Roux-Y jejunal limb was first performed by Longmire in 1951[57]. DuVal[22] has reported 26 patients treated by this method with complete pain relief in 20 patients and weight gain in the entire group. Puestow and Gillesby[83] have modified this technique by amputation of the tail of pancreas followed by splitting the pancreatic parenchyma and pancreatic duct longitudinally to allow better drainage of the pancreatic ductal system into the jejunal Roux-Y. They reported 4 patients with chronic pancreatitis treated by this method with excellent results. It would seem apparent from these reports that adequate pancreatico-jejunostomy will afford free flow of pancreatic secretions into the gastrointestinal tract and thereby relieve abdominal pain, improve pancreatic function and prevent the progression of chronic pancreatitis.

Total Pancreatectomy. Total pancreatectomy for severe chronic pancreatitis was first performed by Claggett in 1944[102]. A limited number of these procedures successfully performed have since been reported in the literature[13,56,87,103]. This procedure has been reserved for those cases of severe calcific pancreatitis with intractible pain, loss of pancreatic exocrine and endocrine function, and failure of other measures to control the disease.

Summary. The problem of pancreatitis has been reviewed in light of recent experimental evidence and clinical experience. The experimental studies of the past decade lend support to

the older concepts of the pathogenesis of pancreatitis particularly as to the importance of the role of a common channel in relation to biliary reflux, the role of bile in the activation of trypsinogen and the action of trypsin on the pancreas and its vascular supply. Other studies have emphasized the importance of pancreatic stasis secondary to pancreatic duct obstruction and superimposed ischemia independent of the bile factor in the genesis of severe pancreatitis. It would appear that a number of factors occurring in sequence are involved in the development of pancreatic necrosis, those being (1) obstruction to the outflow tract of the pancreas, (2) stimulation of pancreatic secretion, (3) activation of trypsinogen to trypsin within the pancreas, (4) general severe ischemia due to the action of trypsin on the vasculature of the pancreas, and (5) widespread pancreatic necrosis due to the final attack of trypsin on the ischemic pancreatic parenchyma.

Recent contributions to the therapy of acute pancreatitis have emphasized the importance of vigorous replacement of the large deficits in blood plasma and red blood cells which occur in the initial phases, the value of antibiotic therapy in controlling the secondary invasion of bacteria and the possible value of the adrenal corticoids in the management of the disease.

A number of surgical procedures are now available for the control of chronic pancreatitis, each designed to correct a particular factor in the pathogenesis of the disease. The selection of appropriate corrective measures will depend on a careful evaluation of the problem not only in relation to the pancreas but also associated organ systems.

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PROCEEDINGS OF

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SEMINAR ON PHYSIOLOGY OF THE EYE

Some Aspects of Binocular Vision. FRANCIS H. ADLER, M.D., (Department of Ophthalmology, University of Pennsylvania Medical School). If two different contours, such as the pictures of a bird and a cage, are viewed in a stereoscope by a normal individual, they will be seen simultaneously and unified, that is, the bird will appear inside the cage. This has been called simultaneous macular perception, or first degree fusion. It is inferred from this that the brain can fuse dissimilar contours imaged on the two foveas.

Closer examination of this phenomenon reveals the fact that this is not so. While the bird is seen "in the cage," it will be noted that where the bars of the cage cross the contour of the bird the whole bar is not visualized. Either the contour of the bird or that of the cage is seen, but not both simultaneously. There is always retinal rivalry for dissimilar foveal images. If the bars of the cage overlying the bird are eliminated, and only the outline considered, the bird and the cage are seen simultaneously. A foveal image of one eye can be fused with a perifoveal image of the other. This poses the question, how far from the fovea of one eye must a contour be in order that it can be fused with a foveal image of the opposite eye?

A method is presented for determining the area in which dissimilar contours can be fused instead of producing retinal rivalry. Using the data for the schematic eye this averages 300 μ in diameter. This corresponds well with the diameter of the rod-free region of the macula as determined by Polyak and by Pirenne. It also corresponds with the area of the fovea (250 μ) previously determined by Adler and Meyer in which visual acuity is at a maximum, and which apparently is used as a unit. The foveal image oscillates over this area due to the normal micronystagmus of the eyes. Seeing is compared to palpating the surface with sensory receptors such as a finger when used to feel a surface. It is suggested that the different types of connections between the receptors of the fovea and those of the perifoveal areas with the brain are the basis of this phenomenon.

Some Aspects of Extraocular Muscle Physiology. GOODWIN M. BREININ, M.D., (Department of Ophthalmology, New York University-Bellevue Medical Center). A number of problems in ocular motility are under investigation. 1) The existence of tonic innervation to the extraocular muscles is a salient feature of electromyographic investigation. This activity is intimately associated with the arousal mechanism and, probably, the reticular formation. In sleep and anesthesia, in man and cat, the electrical activity disappears but returns on awakening. The state of tension of the muscle also plays a part, in that completely relaxed, detached muscle in man was electrically silent but could fire well on versions. No phasic stretch mechanism could be

demonstrated. 2) The action of succinylcholine on extraocular muscle is to elicit a depolarization with induced discharges for several minutes followed by a nonelectrical contracture. A strain gauge, EMG technique shows the effect to be similar in man, dog and cat. The rise of intraocular pressure after succinylcholine is dependent upon compression of the globe by the extraocular muscles. 3) A new law of ocular motility has been proposed. This states that the innervation to the extraocular muscles parallels the position of the eye and can be predicted. Exceptions occur in cocontraction, certain neurological conditions, mechanical strabismus and pseudopalsies.

Some Aspects of Lens Metabolism in Diabetes. JOEL B. CHODOS, M.D., and HEDWIGE E. HABEGGER-CHODOS, M.D. (Wills Eye Hospital). The transport of glucose across cell membranes and the mediation of intracellular enzymatic processes are presently considered to be the main functions of insulin, which should be correlated with the anatomy and biochemistry of the lens. Lack of insulin results in grave repercussions on the lens and may be explained in the light of this knowledge. There is ample experimental evidence that the oxidative breakdown of carbohydrates takes place exclusively in the lens epithelium, furnishing the rest of the lens with high energy compounds. Glycolysis is ordinarily confined to the cortex and nucleus. This energy is required by the lens for protein turnover and maintaining an ionic equilibrium. The diabetic lens is characterized by a deranged carbohydrate metabolism even in the primary phases, and a 71% decrease in hexokinase activity as well as an 83% increase of adenosine triphosphatase activity above normal are noted. The net result is a reduction of available energy. Intumescence of the lens following upon inhibition of carbohydrate metabolism is a secondary phenomenon, and the basic histopathology in the diabetic lens is the hydropic fiber. The action of insulin on the lens is not known and seems to be relatively unimportant in the transfer of glucose across the lenticular membranes. The hypothesis is advanced that insulin mediates intracellular enzymatic processes in the lens epithelial cells. Most, if not all, of the high energy compounds are formed in the lens epithelium and it is logical to assume that the mitochondria in the cells of the lens epithelium play the major role in the formation of high energy compounds such as adenosine triphosphate. Decreased oxidative phosphorylation activity of the mitochondria in the lens epithelial cells in the diabetic state is a most attractive theory but must await experimental confirmation. Furthermore, if the administration of insulin could be shown to exert an influence on the mitochondria, the reversal of diabetic cataracts would find a series of ready explanations.

Some Aspects of Corneal Physiology. FRANCIS P. FURGIUELE, M.D. (Wills Eye Hospital). When the cornea loses transparency by virtue of trauma, excess water or increased pressure, normal passage of light through this medium is distorted interfering with proper image formation on the retina. The factors responsible for the maintenance of normal optical function of the cornea embrace its anatomy, chemical and metabolic physiology and the dynamics concerned with water movement. The anatomic features of the cornea favoring transparency are the mirror-like smoothness of the surface epithelium, the precise lattice-like arrangement of the stromal fibers and surrounding cementing substances. To this may be added its lack of lymphatics and blood vessels. Chemically, 14% of the dry weight of the cornea is made

up of mucins occurring free or bound to acid polysaccharides as mucoids. The free mucopolysaccharides are chondroitin sulphuric acid A, chondroitin and keratosulphate. Studies using radioactive sulphur indicate that the mucopolysaccharides are metabolically active, the major portion of the uptake being related to keratosulphate. The dynamics of water movement and the mechanism by which the cornea maintains a state of deturgescence have been subjected to a great deal of investigation. Cogan and Kinsey had postulated that normal turgescence was maintained by an osmotic gradient across the cornea due to the hyperosmotic effect of tears and aqueous with respect to plasma. Furthermore the epithelium and endothelium were thought to be impermeable to NaCl acting as "limiting barriers." Potts and Maurice, using tracer ions, later showed that NaCl was permeable through these barriers. Recent evidence by Harris suggests that the cornea contains a "water pump or cation pump" mechanism to maintain a normal stage of deturgescence. In addition, this restraining force of hydration appears to be an active process mediated by the living cell. Metabolic enzyme poisons, lowered oxygen and increased CO_2 tension favor corneal hydration by interfering with the "water pump" mechanism.

BOOK REVIEWS AND NOTICES

PRAKTISCHE RHEUMATHERAPIE. By DR. MED. RUDOLF KRON. Pp. 212; 2 ills. Stuttgart: Hippokrates Verlag, 1958. Price, DM 22.50.

THIS book is by a practitioner for practitioners, avoiding expensive tests and procedures. Part I deals with therapeutic methods: elimination of focal infection, salicylates, pyrazoles (pyramidon and butazolidine), hormones (a sound conservatism is revealed), vitamins, chloroquin and gold (both much in favor with the author), irritative substances (pyrogen), physiotherapy, diet; of the substance causing local effect, the author favors injections with isotonic sodium bicarbonate; injections with novocain are useful not because of the anesthetic but because of the inflammatory effect; the value of injecting, locally, antiphlogistic hormones is stressed. Part II presents a description of the rheumatic diseases, as published by the Swiss rheumatic society, and each entity is discussed therapeutically. In presenting Selye's general adaptation syndrome, the author speculates on a pure antiphlogistic and on a pure antiinfectious adaptation. Gold and chloroquin are the chief standbys in rheumatoid arthritis, using the ESR as a guide in management. The chronic deforming polyarthrosis reacts often favorably to pyrogens (the author uses pyrexal which is a liposaccharid obtained from *Salmonella abortus equi*, nonpathogenic for man), management in spas, and chloroquin also being helpful. Special joint localizations are individually discussed. Many neuralgias are caused by spondylosis and spondylarthrosis; and when there is a primary irritative focus in the spine, local peripheral therapy is contraindicated; while neuralgias of peripheral origin tolerate strong local therapy well. Static pains are worse in the evenings, rheumatic pains in the morning, and neuralgic pains at night time. Involvement of the sympathicus nerve may lead to disturbing symptoms referrable to the area of head-neck-chest-upper extremities; gynergen and hydergen are helpful and so is chlorpromazine. Neuralgias of the intercostal nerves and of the abdominal wall offer problems in differential diagnosis. Many helpful suggestions are made for the management of low back pain, sciatica, and herniation of the disc (for the latter condition operation is considered only in urgent cases or as a last resort). Finally, fibrositis, muscular rheumatism, involvement of the nerves and arteries by the rheumatic process are discussed.

Throughout, the author shows sound criticism, humor, understanding for the patients' needs (although psychiatrists will find themselves short changed), he obtains results with small expense to the patient and proves that with his keen and long term observations and with his empirical therapeutic approach, a practitioner can accomplish a great deal.

H.R.

L'ANGIOGRAPHIE CÉRÉBRALE. By JOËL BONNAL, M.D., Assistant Neurosurgeon to The Neurosurgical Clinic of the Faculty of Medicine of Marseille Hospital, AND JACQUES LEGRÉ, M.D., Electroradiologist of the Marseille Hospital. Pp. 254; 223 ills. Paris: Masson et Cie, 1958. Price, 6.00 francs.

THIS book is based on the study of more than 2500 carotid angiograms done since 1949 in the Neurosurgical Clinic of Marseille. The authors state that it is not only a morphological presentation but they hope a dynamic one. An excellent schematic illustration is presented in the beginning of the book of the normal cerebral angiogram. The branches of the vessels are clearly labeled and offer the student the normal pattern which he can compare with the abnormal angiograms to follow. The book is introduced by a short history of the cerebral angiography. The chapter on the technique of cerebral angiography is excellent. In this chapter all the accepted methods of vertebral angiography are discussed as well as unusual techniques such as angiography with compression of the opposite carotid, total simultaneous cerebral angiography and angiography combined with pneumoencephalography, as well as venography and angiography of the orbit.

The whole chapter is devoted to the indications, contraindications, and complications of cerebral angiography. Chapter 3 describes the normal cerebral angiogram and chapter 4 angiography of cerebral malformations and tumors. Chapter 5 presents vascular malformations and 6, angiography of arteriosclerosis and obstruction of arteries and veins. The last chapter, number 7, describes angiographic findings following cranial trauma.

The illustrations in this book are superb and whenever not self-explanatory, they are

accompanied by excellent schematic line drawings.

Although during the past 5 years there have been many new books on cerebral angiography, it is this abstractor's opinion that this is one of the best and should be in the library of the internist, as well as the neurologist and neurosurgeon interested in the ever expanding use of cerebral angiography.

M.S.

DISEASES OF THE ESOPHAGUS. BY J. TERRACOL, Professor of the Faculty of Medicine of Montpellier, and RICHARD H. SWEET, Associate Clinical Professor of Surgery, Harvard Medical School. Pp. 682; 409 ills. Philadelphia and London: W. B. Saunders Co., 1958. Price, $20.00.

SWEET has revised the second edition of Terracol's book, "Les Maladies de L'Esophage." The surgical interests of the revisor led him to concentrate on the problems of endoscopy, biopsy techniques, congenital malformations, extraction of foreign bodies from the esophagus, fistulae, perforations as well as the diagnostic and therapeutic problems associated with esophageal tumors. All of these subjects are thoroughly discussed and the surgical techniques are beautifully illustrated. The new chapter on esophageal substitution is to be commended highly.

From the internists standpoint, the book is extremely deficient in considerations of physiology and pharmacology. Classifications and concepts of motor disorders of the esophagus are obsolete. The authors do not consider reflux from the stomach as a major contributing cause to the development of chronic esophagitis, which is at variance with current concepts. Most amazing to this reviewer is the complete omission from the text of any consideration of hiatal hernia. This abnormality is not even listed in the index. This book will be of interest to the endoscopist and surgeon but will have little to offer those interested in diagnosis and nonsurgical therapy of diseases of the esophagus.

S.L.

L'EMBRYOLOGIE DE L'ŒIL ET SA TERATOLOGIE. BY CH. DEJEAN, G. LEPLAT AND FR. HERVOUËT. Pp. 728; 534 ills. and 10 color plates. Paris: Masson et Cie, 1958. Price, 8.000 fr.

THIS year's monograph published by the Societe francaise d'ophthalmologie presents an exhaustive review of the current knowledge concerning the embryology and teratology of the eye.

The first section contains a detailed descriptive analysis of the development of the normal eye. Special emphasis is placed upon recent theoretical and experimental evidence which has resulted in a better understanding of the mechanisms involved in the differentiation and organization of these tissues. Much of the text is based upon studies carried out by the authors themselves, although a liberal bibliography is included.

The second portion of the book deals with the various results of abnormal growth and development of the eye. The authors have compiled an extensive atlas of teratology and have amplified it with a detailed analysis of the divergent theories offered to explain these malformations.

The work should serve as a useful reference for the clinician as well as for the basic scientist.

W.F.

SURGERY IN WORLD WAR II. ORTHOPEDIC SURGERY IN THE MEDITERRANEAN THEATER OF OPERATIONSS. Edited by COL. JOHN BOYD COATES, JR., MC, MATHER CLEVELAND, M.D., AND ELIZABETH M. MCFETRIDGE, M.A. Pp. 368; 96 ills. Washington: Office of the Surgeon General, Department of the Army, 1957. Price, $4.00.

HISTORICALLY this book covers an era from November of 1942 until May, 1945. During this time 79,000 cases of orthopedic type were treated. The management of these by a Medical Corps of almost no officers of previous combat experience is honestly recorded. The text for peace-time students and physicians may not have extreme medical interest because of the administrative considerations which fortunately are not extensive. The principles evolved from this theater in regard to splinting, management of compound fractures, wounds of joints and amputations are excellent. It would be well to show them to our current and future medical students not only from the standpoint of trauma management but in the big picture if war should again occur. Certainly those responsible for civilian defense from the therapy aspect should know them.

All in all this is a good text which I consider a must for those in the Medical Corps of the Army and Navy or Civilian Defense. It would be well to have its conclusions as to principles of wound management stressed in our current medical school curriculum.

A.S.

AVIATION MEDICINE. Edited by CLAYTON S. WHITE, W. RANDOLPH LOVELACE, II, AND FREDERIC G. HIRSCH. The Lovelace Foundation for Medical Education and Research, Albuquerque, New Mexico. Pp. 276; 109 ills. New York: Pergamon Press, Inc., 1958. Price, $12.00.

THIS book is a valuable presentation of recent advances in instruments and methods. It presents the present state of our knowledge in several fields relating to aviation medicine. The presentations are in the nature of authoritative reviews by persons of considerable stature in their several areas of research. The volume can not only serve as a source book but it can be useful to graduate students and those concerned primarily with research. Individuals interested in respiratory gases will find the chapters on this subject particularly rewarding. M.O.

LE PNEUMOTHORAX SPONTANÉ NON TUBERCULEUX DE L'ADULTE ET SON TRAITEMENT. BY ANDRÉ MEYER, J. P. NICO AND J. CARRAUD. Pp. 144; 32 ills. Paris: Masson et Cie, 1958. Price, 1.950 fr.

THIS is a discussion of spontaneous nontuberculous pneumothorax based upon 53 cases observed between 1949 and 1954 at L'Hôpital Boucicaut. These cases were encountered among 20,000 chest cases seen per year. At the same time 4 cases of spontaneous pneumothorax associated with tuberculosis were encountered. There is an adequate presentation of the etiology, the clinical picture and diagnostic and therapeutic procedures. The authors recommend talc poudrage for recurrent pneumothorax and simple pneumothorax with generalized emphysema. K.B.

PRACTICAL DERMATOLOGY. BY GEORGE M. LEWIS, M.D., Professor of Clinical Medicine (Dermatology) Cornell University Medical College; Attending Dermatologist, The New York Hospital. 2nd ed. Pp. 363; 121 ills. Philadelphia and London: W. B. Saunders Co., 1959. Price, $8.00.

THE second edition of Lewis's Practical Dermatology continues to be a most acceptable small volume for medical students and for general practitioners, as well as an aid in orientation for other specialists. This new edition is improved by the inclusion of some basic science material, which, although sketchy, is most welcome. There has been an increase of 99 plates and 50 pages of text. This additional space has allowed for the inclusion of an increased number of diseases. The illustrations are superb, although black and white for economical reasons; the text is up-to-date; the index is reasonably complete and there is a basic bibliography chiefly of textbooks dealing with dermatology and allied fields. H.B.

TUMORS OF THE LUNGS AND MEDIASTINUM. BY B. M. FRIED, M.D., Associate Attending Physician, Montefiore Hospital; Associate Visiting Physician, Morrisania City Hospital, New York. Pp. 467; 235 ills. Philadelphia: Lea & Febiger, 1958. Price, $13.50.

THE author, who has been interested in tumors of the thorax for more than thirty years, has given us a very good monograph on that subject. With special emphasis on cancer of the lung, he has gone into the histogenesis, pathologic classification, and etiology, as well as the clinical manifestations of the disease throughout its life cycle. Five contributing authors have covered the special problems of therapy. The book is well written and unusually well illustrated from the pathologic viewpoint. The book will be most useful to the student of this field. J.J.

CHRONIC BRONCHITIS, EMPHYSEMA AND COR PULMONALE. BY C. H. STUART-HARRIS, M.D. AND T. HANLEY, M.D., University of Sheffield, England. Pp. 245; 61 ills. Bristol: John Wright & Sons, Ltd. (The Williams & Wilkins Co., Baltimore, exclusive U.S. Agents), 1957. Price, $8.50.

CHRONIC bronchitis and its sequelae, emphysema and cor pulmonale have long been recognized as major medical problems by British authors. American physicians, with certain exceptions, tend to belittle the importance of bronchitis. It is quite possible that a Death Certificate signifying "Bronchitis" would be returned as incomplete or inaccurate. Granted important differences in climate and household heating arrangements between America and Great Britain, one wonders whether this country can be as free from bronchitis as many would imply.

Stuart-Harris and Hanley have produced a short lucid account of the problem. The clinical and pathological pictures of bronchitis, emphysema and cor pulmonale are well summarized. Treatment is clearly presented. Pulmonary function tests are reviewed and the results presented for various stages of the disease process. Surveys of hospital

patients, industrial workers and a rural population are of special interest.

The final chapter on "Epidemiology and Pathogenesis of Chronic Bronchitis" is most provocative. Many unanswered questions regarding air pollution are raised. There can be little doubt that avoidable smoke (tobacco) and less easily avoidable irritant (air pollution) both play major roles in the life history of this increasingly important group of related diseases.

The book is well printed, the majority of the illustrations are clearly reproduced; a few charts and legends are difficult to decipher. References to the literature follow each chapter, an Index is provided. The book is recommended to practitioners as an excellent survey of the subject, and to specialists for some new approaches to an old problem.

R.C.

PERSONALITY PATTERNS OF PSYCHIATRISTS. BY ROBERT R. HOLT, PH.D., AND LESTER LUBORSKY, PH.D. VOL. 1. A STUDY OF METHODS FOR SELECTING RESIDENTS. Pp. 386. New York: Basic Books, Inc., 1958. Price, $7.50. VOL. 2. SUPPLEMENTARY AND SUPPORTING DATA. Pp. 400. Ann Arbor: Edwards Brothers, Inc. Price, $4.00.

VOLUME 1 describes selection procedures for psychiatric residents. It represents the culmination of a 10-year effort to learn how residents were being selected for the Menninger School of Psychiatry. The volume is divided into four parts. Part I introduces the problem, the subjects, and the setting in which they were trained and the research was carried out. Part II describes the plans and main findings of the two major research designs followed. Part III is devoted to the personality of the psychiatrist. The final section offers conclusions and recommendations for the selection of both psychiatric residents and candidates for learning in psychoanalysis.

This book is a worthy contribution to the literature for selection of people for training in psychiatry and in psychoanalysis.

Volume 2 contains detailed accounts of the research methods and many tables of quantitative findings. It is arranged as a series of appendices to the chapters of Volume I, and should be read in connection with these chapters at the points indicated in the text.

This volume contains detailed consideration of measures of competence in psychiatric work and full details of the methods used in obtaining criteria. The book includes samples of the manuals developed for the scoring of interviews and projective texts for psychiatric selection. Included is an extensive summary of expert opinion on the personality requisites for psychotherapy and psychoanalysis. The authors include a full discussion of sources in their results.

M.B.

MODERN CHEMOTHERAPY OF TUBERCULOSIS. BY ROGER S. MITCHELL, M.D., AND J. CARROLL BELL, M.S., Colorado Foundation for Research in Tuberculosis and the University of Colorado School of Medicine, Denver, Colorado. Pp. 109; 11 ills. New York: Medical Encyclopedia, Inc., 1958. Price, $4.00.

IN just over a decade the introduction of effective chemotherapy has revolutionized the treatment of tuberculosis. Three major or standard drugs are available (Streptomycin, Para-aminosalicylic acid and Isoniazid) plus a score of "second choice" or experimental compounds. This concise volume, the eleventh of a series of Antibiotics Monographs is a distillation of the tremendous volume of laboratory research and clinical experience that has accumulated concerning antituberculosis drugs.

The authors summarize the pharmacology, dosage, toxicity, indications and contraindications of all important drugs. Various combinations and regimens are compared. Drug resistance and infection with atypical mycobacteria receive appropriate attention. Supplementary measures: rest, collapse, resection, steroid hormones and patient education (best carried out in a tuberculosis hospital) are intelligently discussed. References (510) add greatly to the value of the book.

This monograph should be studied, and its principles followed, by all physicians who treat tuberculosis.

R.C.

REVERSIBLE RENAL INSUFFICIENCY: DIAGNOSIS AND TREATMENT. BY DONALD H. ATLAS, M.D., PH.D., Associate Professor of Medicine, Northwestern University School of Medicine, and PETER GABERMAN, M.D., Late Associate Professor of Medicine, Chicago Medical School. Pp. 233; 19 ills. Baltimore: The Williams & Wilkins Co., 1958. Price, $7.00.

FROM the mass of literature on acute and chronic renal insufficiency and from their own experience, the authors have presented salient facts about renal insufficiency. They emphasize that the major objective of the book is to enable the clinician to differentiate

these potentially reversible acute and chronic renal insults from primary renal disease where progression is not influenced by treatment, and in this they have been successful.

In the early chapters, pathology, pathogenesis, diagnosis and differential diagnosis of acute renal insufficiency are reviewed as an introduction into the clinical management. The latter chapters, about one-fourth of the book, deal mainly with disturbances in calcium metabolism which are associated with chronic renal insufficiency, and in which the renal disease may be arrested or reversed. Case histories illustrate some of the etiologic factors associated with potentially reversible acute and chronic renal insufficiency.

This book should prove of value to the intern, resident, internist and surgeon. The Bibliography is comprehensive. I.G.

Physiologie du Systeme Nerveux Central. By Georges Morin, Professor of Physiology, Faculty of Medicine, University of Marseille. 3rd ed. Pp. 396; 104 ills. Paris: Masson et Cie, 1958. Price, 3.400 fr.

The author states that although the present edition follows the preceding one in much of the material, he has also made many important additions and changes in order to keep pace with the latest developments in this field.

The chapter on muscular tonus has been revised and includes the most recent knowledge on the musculo tendon proprioceptors. Many changes have been made in the chapters devoted to the hypothalamus, gray central nuclei and the reticular formation. The book is divided into the following chapters: 1) The spinal nerve roots, 2) Spinal cord, 3) Muscular tonus, 4) The cerebellum, 5) The cerebral cortex, 6) The thalamus, 7) The hypothalamus, 8) The basilar gray nuclei, 9) The reticular formation.

This book written in French by a physiologist is primarily concerned with the physiology of the nervous system and not with physiologic anatomy or physiopathology.

This volume is a welcome addition to current textbooks in neurophysiology.

M.S.

Personality Change and Development as Measured by the Projective Techniques. By Molly Harrower, Ph.D., Temple University Medical Center, Pp. 383, illustrated. New York: Grune & Stratton, Inc., 1958. Price, $10.00.

The author, long a leader in the application and refinement of psychological tests, addresses herself to several lingering and important issues in this book. Do these techniques reflect the personality change noted by clinicians or established on some other basis? Harrower, after analyzing the test protocols of a number of patients she has reexamined over the years, concludes that they do. Having settled the basic question, the author goes on to document in some specificity the various dimensions which accompany positive and negative behavioral change. Finally she notes that the kinds of change wrought by psychotherapy, and the changes brought about by time itself or improved life circumstances, or both, are essentially of the same order. While one can argue that the volume falls short of scientific rigor and precision, this is characteristic of the field itself. Even so, this study does mark another step in the evolution of objective assessment techniques. M.B.

Atlas Intracardialer Druck Kurnen. Atlas of Intracardiac Pressure Curves. Atlas de Curvas Tensionales Intracardiacas. By Otto Bayer and Hans Helmut Wolter, Chief and Associate, Medical Department, Berlin-Moabit City Hospital. English translation by G. R. Graham, M.D., London; Spanish translation by Dr. E. Low-Maus, Barcelona. Pp. 185; 53 figs, 42 plates. Stuttgart: Georg Thieme Verlag, 1959 (Intercontinental Medical Book Corp., New York, U.S. Agents). Price, $16.20.

Both the publisher and authors deserve the highest praise for bringing forth this beautiful book.

It consists of three parts, each written in German, English and Spanish. Although it was not the authors' intention, the reviewer knows no less painful way of learning a foreign scientific language.

The first part contains a general discussion of normal pressure curves, illustrated by 23 figures; the second abnormal curves illustrated by 30 figures; the last an atlas of 42 figures illustrating the normal and abnormal pressure patterns in congenital and acquired heart disease (primarily mitral, tricuspid and pericardial) and some artifacts. An attached tape marker (so common in the finer books of years ago) facilitates exposure of the figures referred to in the text. Left and combined left and right heart catheterization is not discussed or illustrated probably because they were not practiced at the time this new

book was written, a tribute to the rapidity of medical advances today.

The major criticism is the lack of anatomic evidence to support the interpretation of the pressure curves. This is particularly true of the wedge pressure curves. L.S.

Die Wirbelsaule in Forschung und Praxis. (Edited by Prof. Dr. med H. Junghanns, Oldenburg): Referatenband II and III, 1958 (Volumes 8 and 10) Edited by Dr. med. F. Biedermann. Pp. 175 each. Stuttgart: Hippokrates Verlag, 1958. Price, not given.

These are volumes 8 and 10 of a series of books entitled "The Vertebral Column in Research and Practice." While most previous volumes dealt with the pathology, diagnosis and treatment of diseases of the spine, the present volumes, like volumes 4 and 6, contain individual reviews of a total of 262 papers and 14 books of the world literature, as well as two collective reviews on the drug therapy of chondrosis intervertebralis by W. Diener, and on the anatomy and pathology of the segments of motion of the spine by E. Emminger. In order to facilitate filing of the reviews, one-sided printing and the international decimal classification were used. All physicians who are interested in the spine will be delighted with this new venture. W.E.

Diseases of the Colon and Anorectum. By Robert Turell, M.D., of the Mount Sinai, Montefiore and Bronx Municipal Hospitals and Associate Professor of Clinical Surgery, Albert Einstein College of Medicine, 2 vols. Pp. 1238; 634 ills. Philadelphia: W. B. Saunders Co., 1959. Price, $35.00.

The author, together with 81 other contributors, has written the best text on the lower segments of the gastrointestinal tract that this reviewer has read. The excellent balance of basic considerations of anatomy, physiology and pharmacology together with the clinical aspects of diagnosis and treatment are unusual for a specialized, surgical text. Even more unusual is the emphasis placed upon emotional aspects of disease, too often anathema to the surgeon.

Many of the contributors are recognized authorities in their fields and all have contributed to the literature of the subject they discuss. Thus there is an up-to-dateness of the material as well as a critical analysis of medical and surgical concepts. The senior author has done an excellent job of integrating the subject material but this reviewer would like to suggest, should the text be re-edited, that the section on diagnosis be expanded. The book is generously illustrated and tersely written. It will be a rewarding reference for student, investigator, teacher, internist and surgeon. S.L.

How to Relax and Have Your Baby. By Edmund Jacobson, M.D. Pp. 187; 16 pages of illustrations. New York: McGraw-Hill Book Company, Inc., 1959. Price, $3.95.

Jacobson's method of controlled scientific muscle relaxation during pregnancy and labor is somewhat in contrast to the frenetic exercise and study program usually advised as preparation for "natural childbirth." He contends that exercise produces muscular tension rather than relaxation but that the latter, which is so desirable during labor, can be achieved by application of the principles he has developed during the years he has studied muscle physiology. Muscle relaxation is quite different from hypnosis since it is under the control of the patient and in contrast to the usual training programs during pregnancy. The author makes no effort to acquaint the mother with details of pelvic anatomy and physiology.

The method of relaxation is described in great detail as it would be taught to a patient during pregnancy. Methods for relaxing each set of muscles in the body are explained and well illustrated with photographs. Finally, the technique for achieving relaxation during labor and after delivery is indicated.

There is no doubt but that relaxation and elimination of tension will improve labor and delivery. This book should be of great help to doctors and patients who are interested in "natural childbirth" but who are loath to accept all the ritual and mumbo-jumbo which has heretofore been a part of the program. J.W.

Mental Subnormality. By Richard L. Masland, M.D., Assistant Director of the National Institute of Neurological Diseases and Blindness, National Institutes of Health, Seymour B. Sarason, Ph.D., Professor of Psychology, Yale University, and Thomas Gladwin, Ph.D., Social Science Consultant with Community Services Branch of the National Institute of Mental Health. Pp. 442; 11 ills. New York: Basic Books, Inc., 1958. Price, $6.75.

A PHYSICIAN, a psychologist and a social scientist present the results of an intensive research investigation, sponsored by the National Association for Retarded Children, into the biological, psychological and cultural factors in the causation of mental subnormality.

Part one of the volume deals with those factors which produce anatomical or chemical abnormalities of the nervous system leading to mental subnormality. Part 2 is a study of the cultural and environmental factors which, through the establishment of unhealthy intellectual response, may prevent the optimum functioning of the mind in a person whose nervous system is basically capable of normal activity.

The mentally subnormal population is at the lower end of a continuum of intellectual ability which embraces the total population. The authors state that the challenge lies in the realization that the more known about mental subnormality the more will also be known about normal intellectual processes.

Extensive reference lists and an index is included. The entire book is unusually well written and makes for stimulating reading.

M.B.

EL ORIGEN DE LAS BACTERIAS. (THE STARTING POINT OF BACTERIA). BY C. XALABARDER AND R. CULLELL, El Instituto Antituberculoso, Barcelona, Spain. Pp. 95; 76 ills. Barcelona, Spain: Instituto Antituberculoso "Francisco Moragas," 1958.

THE authors conceived the idea of killing bacteria with formalin shortly after starting new broth cultures, and of taking electronmicrographs of these very young cultures. The bizarre fungoid structures observed are interpreted as meaning that bacteria are microfungi; rod forms being arthrospores and cocci being conidia.

The text is limited to a few pages and repeated in English, as are also the legends with the photographs. There are technically good pictures of several kinds of bacteria, but the interpretations made by the authors are far from satisfactory to this reviewer.

Electron microscopists should have a look at these photographs, without reading the text.

E.S.

LISTERIOSEN. Edited by E. ROOTS AND D. STRAUCH, Justus Liebig University, Giessen, Germany. Pp. 116; 15 ills. Berlin: Paul Parey, 1958 (Can be ordered through Walter J. Johnson, Inc., New York). Price, DM 14. ($3.34).

IN this paper-bound monograph are printed the 11 papers delivered at a 2-day international symposium on listeriosis held at Giessen, June 27–28, 1957. Three articles are written in English, the others in German.

L. monocytogenes, and the host-parasite relationships it establishes in animal and man, are subjected to thorough examination and informal discussion. Not much new information on the organism itself or the nature of listeriosis in lower animals comes from this symposium. But this reviewer found the evidence for a relationship to human abortion worthy of note. Finally, it should be pointed out that *L. monocytogenes* is still a candidate for the unsettled etiology of infectious mononucleosis in the opinion of some of the participants of the symposium.

The contents of this monograph have appeared as supplement No. 1 of the Zentralblatt für Veterinarmedizin.

E.S.

LINFOPATIAS TUMORALES (Lymphatic Tumors). BY MANLIO FERRARI, Professor of Pathology, Montevideo School of Medicine; Internist, Institute of Pathology and Physical Sciences, and HELMUT KASDORF, Associate Professor of Radiology, Montevideo School of Medicine; Therapist, Institute of Radiology and Physical Sciences. Pp. 199; 70 ills. Buenos Aires, Argentina: Lopez & Etchegoyen, 1958.

IN this book giant follicular lymphoblastoma, lymphosarcoma, Hodgkin's disease, reticulum cell sarcoma and undifferentiated lymphatic sarcoma are thoroughly discussed. Emphasis is placed upon the various clinical manifestations of these tumors. The series of cases is relatively large and the authors' experiences are similar to those reported by other investigators. The last chapter is devoted to a summary of the different accepted forms of treatment. No new drugs or methods of treatment are discussed.

F.C.

THE LOVE OF A PHYSICIAN: GEORGE E. PFAHLER, PIONEER RADIOLOGIST. BY MURIEL B. PFAHLER. Pp. 274; 4 ills. Philadelphia: Dorrance & Co., 1958. Price, $3.75.

"The Love of a Physician" is a beautiful narrative of the life of George Edward Pfahler as seen by and recorded by his wife, Muriel B. Pfahler. The author has in the 274 pages drawn a word picture of Dr. Pfahler, the man, a devoted husband, but more especially his all-consuming love and devotion for the field of Radiology.

The story of George Edward Pfahler as told by Mrs. Pfahler is a saga of the discovery and development of the Roentgen ray. An extensive diary kept by the author, together with the characteristic records kept by her husband provided the material for the book. Mrs. Pfahler, by quoting extensively from the words and writings of Dr. Pfahler has made the volume a documentary recording of the growth of Radiology. In addition she has interwoven intimate details of events in the life of Dr. Pfahler so as to give substance to the title "Love of a Physician." The reviewer sees in this volume a delightful picture of a true romance in medicine as could only be told by a devoted wife.

Those of us who have had the privilege of intimate contact with Dr. Pfahler over the years are grateful to Muriel Pfahler for her having given to us this memorial of a great man, a physician, scientist and humanitarian. F.B.

PHYSICAL DIAGNOSIS. By JOHN A. PRIOR, M.D., Professor of Medicine, and JACK S. SILBERSTEIN, M.D., Clinical Associate Professor of Medicine, Ohio State University College of Medicine. Pp. 363; 193 ills. St. Louis: The C. V. Mosby Company, 1959. Price, $7.50.

THIS first edition represents a good, easily read and comprehended text on physical examination. It contains more information about history taking than most such books. It is intended for the beginner. It is recommended for medical students. W.S.

THE PASTEUR FERMENTATION CENTENNIAL 1857–1957. Edited by MILTON MELTZER. Pp. 207; 20 figs. and 8 photographs. New York: Charles Pfizer & Co., Inc., 1958.

IN the fall of 1957, Charles Pfizer & Company arranged a symposium to commemorate the publication of Louis Pasteur's momentous paper reporting that the fermentation of lactic acid is a biological process. With this discovery the science of microbiology was born. It would have been futile to attempt in a one-day symposium to do justice to all of the developments in microbiology that occurred in the ensuing one hundred years.

Instead, the program was restricted to three areas. "The first, appropriately enough, dealt with fermentation, and Marvin Johnson of the University of Wisconsin handled this most capably by an excellent paper and by a panel discussion on modern research in this field. Under the circumstances it was inevitable that one of the topics would be "Trends in Antibiotic Research." This part of the program could easily have been sterile, but it was not. The six papers on antibiotics, including one each from Cuba, U.S.S.R., and Japan, combine widely different aspects such as genetics (Demerec), anticancer (Gause) and mechanism of penicillin action (Strominger) to produce a kaleidoscopic picture of present and future research in certain parts of the world.

The third part of the program was assigned to host-parasite relationships, a subject unrelated to the other two but readily justified by Pasteur's pioneer work on immunization. Rene Dubos and four other investigators, including Derrick Rawley from England, discussed cellular and biochemical interplay between host and parasite in a competent and lively manner. Readers interested in the work of these people, as well as that of W. W. Ackerman, L. J. Berry, or D. E. Rogers will find in this section interesting and satisfying summaries.

As far as this reviewer can determine, this book can be obtained only from Chas. Pfizer & Co., Inc., New York. Interested persons should contact the company directly.

E.S.

BIOLOGICAL ASPECTS OF CANCER. By JULIAN HUXLEY, F.R.S. Pp. 156. New York: Harcourt, Brace and Co., 1958. Price, $3.75.

THIS concise volume written by a well-known biologist is a broad survey of the problem from a biological standpoint. It brings a refreshing point of view to an extremely complex problem. The various biological aspects are scrutinized with considerable documentation in various fields including a comparative distribution of neoplasms in plants, lower and higher animals. This type of approach is seldom encountered. Frequently the oncologist loses the true perspective of cancer as a biological problem. The genetics, the viral origin, and the endocrine aspects of cancer are all surveyed in this splendid little monograph. The author clearly attempts to synthesize the various approaches to the problem without any claim at being an authority on some of the more technical aspects of cancer research. This monograph is recommended not only to the mature oncologist, but particularly to the young investigator who is beginning the study of a complex problem. This monograph will deter him from being bogged down in some relatively insignificant portion of a comprehensive biological problem. V.M.

A Color Atlas of Morphologic Hematology. By Geneva A. Daland, B.S., Chief Laboratory Assistant in Hematology, Thorndike Memorial Laboratory, Boston City Hospital. Edited by Thomas Hale Ham, M.D., Professor of Medicine, Western Reserve University School of Medicine. Revised edition. Pp. 72; 9 ills. and 10 color plates. Cambridge, Mass.: Harvard University Press, 1959. Price, $6.75.

The new edition of this well-known color atlas provides a helpful reference guide to the study of blood films in clinical medicine. The descriptions and illustrations of the maturation of the various blood cells are simplified but quite adequate for use in the recognition of abnormal or immature forms in the peripheral blood or bone marrow. There is a comprehensive classification of the anemias, with representative findings given for the most important disorders in this group as well as for the leukemias and infectious mononucleosis.

This volume may be used alone as an introduction to morphologic hematology, but with enhanced value when studied along with its companion book, A Syllabus of Laboratory Examinations in Clinical Medicine (T. H. Ham, Harvard University Press, 1950).

C.Z.

Les Maladies Du Larynx. By J. Piquet, Professor of the Faculty of Medicine, University of Lille, and J. Terracol, Professor of the Faculty of Medicine, University of Montpellier. Pp. 674; 241 ills. Paris: Masson et Cie, 1958. Price, unbound, 8,500 fr.; bound 9,500 fr.

The authors, internationally recognized authorities, have collaborated to produce a volume which is the best in its field and notable for its painstaking organization, lucid text and comprehensive coverage. Rarely, have the anatomy, embryology, histology and pathology of the larynx been presented with such clarity. Readily understandable terms are employed to describe methods of examination including the use of endoscopic, radiographic and tomographic techniques. The discussion of congenital and acquired abnormalities is an important contribution. Every aspect of acute and chronic infection of the larynx is considered from the viewpoint of background and development as well as diagnosis and treatment and with attention to such infrequent lesions as those due to scleroma, pemphigus and hormonal dysfunctions. Strictly factual information is presented concerning the impact of recent advances in chemotherapy upon the current treatment of syphilis, tuberculosis and leprosy of the larynx. The information on traumatic and stenotic lesions and foreign bodies is complete and authoritative. Laryngeal paralyses and tumors are dealt with in meticulous detail. Included in the section on rehabilitation of the laryngectomized patient are discussions of esophageal voice, the use of prostheses and the value of surgical reconstructions. The illustrations are unusually effective and the bibliographies appended to the sections have been selected with discrimination. This book is of importance to laryngologists and those concerned with the diagnosis and treatment of laryngeal disorders. H.S.

Hématologie Clinique. By Jean Bernard and Marcel Bessis. Pp. 526; 295 ills. and 37 color plates. Paris: Masson et Cie, 1958. Price, 14.500 fr.

This is an excellent textbook of hematology written by some of the foremost French workers in this field. The material is presented in 5 major sections, namely, General Hematology, Disorders of Erythrocytes, Disorders of Leukocytes, Hemorrhagic Diseases, and Diagnostics. The latter encompasses largely those hematologic problems not treated in the preceding sections. Physiologic, morphologic and diagnostic aspects of the various blood cell series and their involvement in disease processes are quite adequately discussed. The text is beautifully and extensively illustrated with 295 figures and 37 color plates. There are numerous tables which summarize the main features of many of the hematologic disorders. Although treatment is outlined, this may not be given in sufficient detail for some readers. Otherwise, the volume is a valuable hematology reference work for medical students and physicians who read French. C.Z.

The Middle Ear. By Heinrich G. Kobrak, M.D., Ph.D., Professor of Otological Research, College of Medicine, Wayne State University, with chapters by J. E. Fournier, M.D., John R. Lindsay, M.D., Samuel Rosen, M.D., A. Wilska, M.D., H. Wullstein, M.D., and Fritz Zogllner, M.D. Pp. 254; 240 ills. and 6 color plates. Chicago: The University of Chicago Press, 1959; London: Cambridge University Press, 1959; Toronto: The University of Toronto Press, 1959. Price, $15.00.

THIS classic in its field condenses the current knowledge of every aspect of the middle ear into a single, concise, comprehensive and authoritative volume. The early chapters deal with the significant contributions of the basic sciences. Methods of study of the middle ear, the functions of the sound-conduction mechanism and the practical aspects of these concepts are explored and subjected to critical analysis. Strictly factual accounts are given of new electro-acoustic techniques and new methods of observation of acoustic reflexes. Each author is a world authority in his special sphere. Almost one half of the volume is devoted to otosclerosis and fenestration (Lindsay), mobilization of the stapes and fenestration of the oval window (Rosen), treatment of middle ear deafness by prosthesis (Kobrak), tympanoplasty (Wullstein), and plastic surgery of the sound-conduction system of the middle ear (Zoellner). The authors are thoroughly familiar with patients as well as the literature and basic science, and their practical methods and discriminating insights render this book invaluable to every otologist, while physiologists and those in fields allied to otology will find it an essential reference work. H.S.

Variables Related to Human Breast Cancer. BY V. ELVING ANDERSON, HAROLD O. GOODMAN AND SHELDON C. REED, from the Dight Institute for Human Genetics, University of Minnesota. Pp. 172; 7 ills. Minneapolis: University of Minnesota Press, 1958. Price, $4.00.

THIS small book presents an intensive study of the hereditary factor in breast cancer. The organization of the book is exemplary and the mode of presentation is quite clear. Furthermore, for a book of this type, it is quite readable; the complicated and extensive tables being published in an annex at the back and only those few tables needed to illustrate the points being made appearing in the text. There is a very comprehensive survey of related literature.

For those interested in the problem of breast cancer, this would seem to be a very well controlled study. R.T.

Atlas de Radiologie Clinique de La Presse Médicale. Pp. 400; 1,764 ills. Paris: Masson et Cie, 1958. Price, 4.000 fr.

THIS is an excellent work covering a great variety of subjects with radiological emphasis, from Paget's disease to congenital heart diseases, postbulbar ulcers, and others. In many respects the presentation is superior to the ordinary textbook because each subject has been written by an author expert in the field. Despite the numerous authors and variety of subjects, there is a uniformity in presentation with emphasis on brevity and compactness. It is gratifying to be able to adequately cover a subject in a very short time. The illustrations are excellent. There are valuable references and the idea of compilation of monographs is excellent. H.S.

The Preservation of Youth. BY MOSES MAIMONIDES. Translated from the original Arabic by HIRSCH L. GORDON, M.D., PH.D., D.H.L. Pp. 92. New York: Philosophical Library, 1958. Price, $2.75.

MOSES BEN MAIMON (1135–1204) was born in Cordova, Spain, whence he fled at the age of 13, because of persecution, to Southern Spain. From 23 to 30 he was in Fez, Morocco, where he studied medicine. The rest of his life he spent in Cairo, Egypt, where he achieved fame as a physician. His 10 medical writings, all in Arabic, have heretofore been known only through their translations through Hebrew into Latin. This is the first to be translated directly from the Arabic into English. Written for the Sultan Al Afdal, son of Saladin, it is remarkable for the clarity, simplicity and rational approach which shine through the encumbrance of the current medical lore and preconceptions. R.K.

New Steroid Compounds with Progestational Activity. Ann. New York Acad. Sci., 71, Art. 5. BY ABRAHAM E. RAKOFF AND EDWARD C. REIFENSTEIN, JR., and 56 others. Pp. 327; illustrated. New York Academy of Sciences, 1958.

Doctor Squibb: The Life and Times of a Rugged Idealist. BY LAWRENCE C. BLOCHMAN. Pp. 371; frontispiece portrait. New York: Simon and Schuster, 1958. Price, $5.00.

THE story of the varied life of a "quarrelsome Quaker" doctor, a graduate of Jefferson in 1845, fighting in the Navy, opposing quacks and adulterated drugs, both a crusader and a shrewd business man who founded a great pharmaceutical house. It is largely based on a journal of his daily life that he kept for over 50 years, till his death in October, 1900. Notwithstanding the inclusion of rather frequent trivialities and an annoying failure to cut recurring edges of pages, the book has its value in placing on the record details of a richly varied life and in its appeal to several classes of readers. E.K.

International Journal of Health Education, Vol. 1, Nos. 1 (January) and 2 (April), 1958. Published in English and French. Pp. 64 and 60; illustrated. New York: American National Council for Health Education of the Public, Inc., 1958. Subscription, $3.00 per year.

THIS new journal is the official quarterly organ of the International Union for Health Education of the Public, Paris, France. This nongovernmental organization has as its aim the development of health education throughout the world. Directed to the public, and authored mostly by nonphysicians, this publication will be of interest to all working in the field of health education.

F.R.

Gestation. Transactions of the Fourth Conference, March 5, 6 and 7, 1957. Edited by CLAUDE A. VILLEE, Assistant Professor of Biological Chemistry, Harvard Medical School. Pp. 216; 64 ills., 3 in color. New York: Josiah Macy, Jr. Foundation, 1958. Price, $4.50.

THE Fourth Conference on Gestation, sponsored by the Josiah Macy, Jr. Foundation, was devoted to the discussion of the development and function of various fetal fluids. The participants include anatomists, chemists, physiologists, biologists, pathologists, pediatricians, and obstetricians, many of whom have devoted much time to the study of the problem.

The conferences, and as a result the transactions, are entirely informal and consist of a brief introduction to a specific phase of the subject and general discussion by the participants. Most of the material presented is a result of animal research but much involves human beings. A considerable amount of the information is theoretical and as yet incomplete and, therefore, cannot be applied to practice but in the future will undoubtedly offer solutions to what now are perplexing clinical problems. For instance, the long discussions on the origin and physiology of fetal fluids, the uptake of materials by the yolk sac and on the development of fetal immunity all have great potential value for clinicians.

The transactions of the conferences on gestation are of particular interest to research workers in the field of reproduction and much less valuable to the clinician.

J.W.

L'Annee Endocrinologique. BY M. ALBEAUX-FERNET, L. BELLOT, P. BUGARD, J. CHABOT, J. DERIBREUX, M. GELINET AND J. D. ROMANI. 10th year. Pp. 239; 19 ills. Paris: Masson et Cie, 1958. Price, 2.000 francs.

THIS yearbook reviews progress in Endocrinology under the following headings: Adrenals, Thyroid, Neuro-hypophysis, Testicles, Ovaries, and Endocrine-metabolic problems. Within each section certain aspects are discussed; since the aspects selected are identical each year, the discussion is not necessarily based on publications of the past year, but on significant papers of several years. Unfortunately in two chapters (New Clinical Concepts of Thyroid Insufficiency; Recent Therapy of Thyroid Insufficiency) bibliographical references are absent.

Those who have the time for following the world literature in Endocrinology, will find little of value in this book. Many of us (and this includes the reviewer) will find it useful to peruse this volume, if only to find an interesting publication referred to, which we have otherwise missed.

K.P.

Water and Electrolyte Metabolism in Relation to Age and Sex. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A. M.B., B.CH. AND CECILIA M. O'CONNOR, B.SC., Ciba Foundation Colloquia on Ageing, Volume 4. Pp. 327; 85 ills. Boston: Little, Brown & Co., 1958. Price, $8.50.

THIS is a fascinating symposium on water and electrolyte metabolism. Many of the papers summarize known pertinent information in the field. New contributions aid in the understanding of this complex and important subject. Whereas, some of the articles involve animal research, others report results of clinical research, and should prove to be extremely valuable for the practicing physician and surgeon. Of particular interest are the sections on sodium, potassium and water excess and deficit.

W.P.

The Criminal Mind. BY PHILIP Q. ROCHE, M.D., Assistant Professor of Psychiatry, University of Pennsylvania School of Medicine. Pp. 299. New York: Farrar, Straus and Cudahy, Inc., 1958. Price, $5.00.

As a Psychiatrist for the Eastern State Penitentiary for over 10 years and a Chairman of the Forensic Section and Member of the Legal Aspects Committee of the American Psychiatric Association, Dr. Roche is eminently qualified to survey the role of psychiatry in the criminal courts. This book represents the fifth volume of the Isaac Ray Award Books, the authors chosen because of their distinctive contributions by the American Psychiatric Association.

The author's main theme centers about the significant problem of communication between psychiatry and the criminal law, pointing up the differences in the orientations of both disciplines: criminal law is a moral system; psychiatry is a branch of science, therefore, basically unconcerned about a "right" or "wrong" system of communication. He draws upon highly interesting illustrative case material to crystallize the dissimilarities in these frames of reference.

M.P.

What We Do Know About Heart Attacks. BY JOHN W. GOFMAN, M.D., Professor of Medical Physics, University of California. Pp. 180; 3 ills. New York: G. P. Putnam's Sons, 1958. Price, $3.50.

WRITTEN for the layman, this book describes in popular language a great deal of our recently gained knowledge concerning coronary artery disease. The author believes that wide application of what *is* known could lead to a considerable prolongation of life for susceptible individuals. Susceptibles would be discovered by the detection of two common denominators in the etiology of this prevalent disease. These are: 1) elevation of the so-called Atherogenic Index (based on ultracentrifugal lipoprotein measure-

ment), and 2) elevation of blood pressure. The first of these Gofman believes to be the common denominator in such known etiological factors as familial tendency, sex, overweight, diabetes, and the like. It is susceptible to therapeutic attack by means of diet. The elevation of the Index itself would indicate the need for such therapy, but the variety of lipoprotein elevation would determine the *kind* of dietary management to be employed. Those having elevation of the S_f 0–20 group would be placed on a diet low in saturated fats, whereas those with elevation of the S_f 20–400 group would be restricted in their intake of carbohydrate. Elevation of blood pressure would be controlled by modern drug therapy. The fact that a cooperative study carried out in a number of clinics in the United States has not as yet demonstrated the superiority of the Atherogenic Index over other means of detecting the coronary susceptible does not disturb the author, nor does the recent evidence that stress plays an important role in the etiology of the disease receive any consideration.

T.D.

Nutrition in Health and Disease. By LENNA F. COOPER, B.S., M.A., M.H.E., Sc.D., Consulting Dietitian, Montefiore Hospital; EDITH M. BARBER, B.S., M.S., Food Editor, General Features Syndicate; HELEN S. MITCHELL, A.B., PH.D., Dean, School of Home Economics, University of Massachusetts; and HENDERIKA J. RYNBERGEN, B.S., M.S., Associate Professor of Science, Cornell University-New York Hospital School of Nursing. 13th ed. Pp. 734; 148 ills. Philadelphia: J. B. Lippincott Co., 1958. Price, $6.00.

THE principles of nutrition are presented in the broadest and most practical manner in this volume. The basic biochemical and physiological data concerning food and essential nutrients are briefly, though adequately, reviewed with the aid of appropriate graphs and tables. The experience of the authors in dietetics is reflected in a superlative fashion in the planning of meals and therapeutic dietary programs with considerations given to economic, racial and regional factors involved in food choices. A complete compendium of diets employed in the treatment of various medical and surgical disease with a discussion of the disorders and the basis for the use of the specific diet is a particularly valuable feature of this work. This book is a standard reference for dietitians, nutritionists and should be used by all physicians involved in the care of patients.

C.S.

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